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(54) Title: COMBINATORIAL LIBRARIES OF CYCLIC UREA AND CYCLIC THIOUREA DERIVATIVES AND COMPOUNDS THEREIN

(57) Abstract

The invention provides a rapid approach for combinatorial synthesis and screening of libraries of cyclic urea and cyclic thiourea compounds. The present invention further provides the compounds made by the combinatorial synthesis.

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COMBINATORIAL LIBRARIES OF CYCLIC UREA AND CYCLIC THIOUREA DERIVATIVES AND COMPOUNDS THEREIN

BACKGROUND OF THE INVENTION

FIELD OF THE INVENTION

The present invention relates generally to the combinatorial synthesis of urea derivatives. More specifically, the invention provides novel cyclic ureas and thioureas as well as novel combinatorial libraries comprised of many such compounds, and methods of synthesizing the libraries.

BACKGROUND INFORMATION

The process of discovering new therapeutically active compounds for a given indication involves the screening of all compounds from available compound collections. From the compounds tested one or more structure(s) is selected as a promising lead. A large number of related analogs are then synthesized in order to develop a structure-activity relationship and select one or more optimal compounds. With traditional one-at-a-time synthesis and biological testing of analogs, this optimization process is long and labor intensive. Adding significant numbers of new structures to the compound collections used in the initial screening step of the discovery and optimization process cannot be accomplished with traditional one-at-a-time synthesis methods, except over a time frame of months or even years. Faster methods are needed that allow for the preparation of up to thousands of related compounds in a matter of days or a few weeks. This need is particularly evident when it comes to synthesizing more complex compounds, such as the cyclic urea and thiourea compounds of the present invention.

Solid-phase techniques for the synthesis of peptides have been extensively developed and combinatorial libraries of peptides have been generated with great success. During the past four years there has been substantial development of chemically synthesized combinatorial libraries (SCLs) made up of peptides. The preparation and use of synthetic peptide combinatorial libraries has been described, for example, by Dooley in U.S. Patent 5,367,053, Huebner in U.S. Patent 5,182,366, Appel et al. in WO PCT 92/09300, Geysen in published European Patent Application 0 138 855 and Pirrung in U.S. Patent 5,143,854. Such SCLs provide the efficient synthesis of an extraordinary number of various peptides in such libraries and the rapid screening of the library which identifies lead pharmaceutical peptides.

Peptides have been, and remain, attractive targets for drug discovery. Their high affinities and specificities toward biological receptors as well as the ease with which large peptide libraries can be combinatorially synthesized make them attractive drug targets. The screening of peptide libraries has led to the identification of many biologically-active lead compounds. However, the therapeutic application of peptides is limited by their poor stability and bioavailability in vivo. Therefore, there is a need to synthesize and screen compounds which can maintain high affinity and specificity toward biological receptors but which have improved pharmacological properties relative to peptides.

Combinatorial approaches have recently been extended to "organic," or non-peptide, libraries. The organic libraries to the present, however, are of limited diversity and generally relate to peptidomimetic compounds; in other words, organic molecules that retain peptide chain pharmacophore groups similar to those

present in the corresponding peptide. Although the present invention is principally derived from the synthesis of dipeptides, the dipeptides are substantially modified. In short, they are chemically modified through alkylation, acylation, reduction, and cyclization into the subject ureas, thus providing mixtures and individual compounds of substantial diversity.

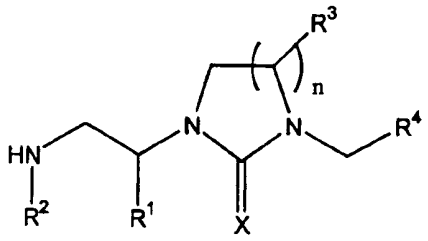
Significantly, many biologically active compounds contain cyclic ureas. Cyclic ureas have been reported by Lam et al., Science, 263:380 (1994), to be useful as inhibitors of human immunodeficiency virus (HIV) protease and HIV replication. Recently, Kim et al., Tetrahedron Lett., 37:5309 (1996), illustrated the synthesis of oligomeric cyclic ureas as a non-natural biopolymer. Because cyclic urea moieties are found in many biologically active compounds and are known to have useful therapeutic implications, there is a need to further study and develop large numbers of cyclic ureas and their binding to biological receptors.

This invention satisfies these needs and provides related advantages as well. The present invention overcomes the known limitations to classical organic synthesis of cyclic ureas as well as the shortcomings of combinatorial chemistry with small organics or peptidomimetics. Moreover, the present invention provides a large array of diverse cyclic ureas which can be screened for biological activity, and as described below, are biologically active.

SUMMARY OF THE INVENTION

The invention provides a rapid approach for combinatorial synthesis and screening of libraries of cyclic urea and cyclic thiourea compounds. The present invention further provides the compounds made by the

combinatorial synthesis. More specifically, the present invention relates to the generation of synthetic combinatorial libraries of organic compounds based on the formula:



wherein R^1, R^2, R^3, R^4, X and n have the meanings provided below.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows the Reaction Scheme I for preparing libraries and compounds of the present invention.

Figure 2 provides the RP-HPLC and LCQ-Mass spectra data for two individual compounds within the subject libraries, one cyclic urea (X = O; Figure 2a and 2b) and one cyclic thiourea (X = S; Figure 2c and 2d).

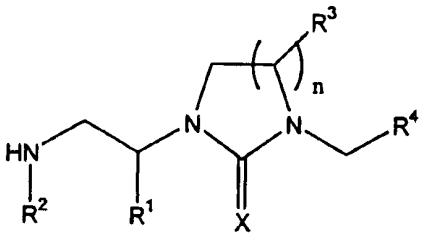
Figure 3 graphically depicts the μ-opioid receptor screening data for the N-benzyl aminocyclic thiourea library of the subject invention (named therein as "DCR 527"). Specifically, Figure 3a provides the μ-opioid receptor assay data for pools 1 to 80 of that library, Figure 3b graphs the results of pools 81 to 117, and Figure 3c depicts the data for pools 118 to 157.

Figure 4 provides graphs depicting the κ-opioid receptor screening data for the N-benzyl aminocyclic

thiourea library (DCR 527). Specifically, Figure 4a graphs the κ-opioid receptor assay data for pools 1 to 80 of that library, Figure 4b provides the data for pools 81 to 117, and Figure 4c is the data for pools 118 to 157.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to the generation of synthetic combinatorial libraries and individual compounds which are based on the Formula I:



FORMULA I

In the above Formula I:

R^1 is a hydrogen atom, C_1 to C_{10} alkyl; C_1 to C_{10} substituted alkyl, C_7 to C_{16} phenylalkyl, C_7 to C_{16} substituted phenylalkyl, phenyl, substituted phenyl, C_3 to C_7 cycloalkyl, or C_3 to C_7 substituted cycloalkyl;

R^2 is C_1 to C_{10} alkyl, C_2 to C_{10} alkenyl, benzyl, substituted benzyl, naphthyl, or substituted naphthyl and, preferably, is methyl, ethyl, benzyl, allyl, or naphtylmethyl, more preferably 2-naphthylmethyl, and R^2 is most preferably methyl or benzyl;

R^3 is a hydrogen atom, C_1 to C_{10} alkyl; C_1 to C_{10} substituted alkyl, C_7 to C_{16} phenylalkyl, C_7 to C_{16}

substituted phenylalkyl, phenyl, substituted phenyl, C_3 to C_7 cycloalkyl, or C_3 to C_7 substituted cycloalkyl;

R^4 is C_1 to C_{10} alkyl, C_2 to C_{10} alkenyl, C_1 to C_{10} substituted alkyl, C_3 to C_7 substituted cycloalkyl, C_7 to C_{16} phenylalkyl, C_7 to C_{16} substituted phenylalkyl, C_7 to C_{16} phenylalkenyl or C_7 to C_{16} substituted phenylalkenyl;

X is an oxygen atom(O) or a sulfur atom(S); and

n is one or two.

In one embodiment of the above cyclic ureas and thiourea compounds, the substituents are as described immediately following Formula I above except that n is one. In another embodiment of the above cyclic ureas and thiourea compounds, the substituents are as described immediately following Formula I above except that n is two and R^3 is other than hydrogen and:

R^3 is selected from the group consisting of C_1 to C_{10} alkyl; C_1 to C_{10} substituted alkyl, C_7 to C_{16} phenylalkyl, C_7 to C_{16} substituted phenylalkyl, phenyl, substituted phenyl, C_3 to C_7 cycloalkyl, and C_3 to C_7 substituted cycloalkyl.

In yet another embodiment of the above cyclic ureas and thiourea compounds, the substituents are as described immediately following Formula I above except that n is two and:

R^4 is selected from the group consisting of 1-phenyl-1-cyclopropylmethyl, 2-phenylbutyl, 3-phenylbutyl, *m*-tolylethyl, 3-fluorophenethyl, 3-bromophenethyl, (α,α,α-trifluoro-*m*-tolyl)ethyl, *p*-tolylethyl, 4-fluorophenethyl, 3-methoxyphenethyl, 4-bromophenethyl,

4-methoxyphenethyl, 4-ethoxyphenethyl, 4-isobutyl-α-methylphenethyl, 3,4-dichlorophenethyl, 3,5-bis(trifluoromethyl)phenethyl, 3-(3,4-dimethoxyphenyl)propyl, 4-biphenethyl, 3-phenyl-2-methyl-2-propenyl, 3-(2-trifluoromethylphenyl)-2-propenyl, 3,4-dimethoxyphenethyl, 3,4-(dihydroxy)phenylethyl, 3-(2-methoxyphenyl)-2-propenyl, benzyl, 3-(4-chlorophenyl)-2-propenyl, *trans*-phenyl-2-propenyl, *m*-xylyl, phenethyl, 3-phenylpropyl, 4-phenylbutyl, 3,5-bis(trifluoromethyl)benzyl, butyl, heptyl, isobutyryl, (+/-)-2-methylbutyl, isovaleryl, 3-methylvaleryl, 4-methylvaleryl, 2-butenyl, 3-butenyl, *p*-xylyl, neopentyl, *tert*-butylethyl, cyclohexylmethyl, cyclohexylethyl, cyclohexylbutyl, cycloheptylmethyl, ethyl, 2-methyl-1-cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, 3-cyclopentylpropyl, cyclohexanepropyl, 4-methyl-1-cyclohexylmethyl, 4-*tert*-butyl-1-cyclohexylmethyl, 4-methylcyclohexylethyl, 2-methyl-2-butenyl, 1-adamantylethyl, 2-(α,α,α-trifluoro-*m*-toluidino)-3-pyridylmethyl, 4-nitrophenethyl, 4-(nitrophenyl)butyl, 3-(4-nitrophenyl)-2-propenyl, 2-nitrobenzyl, 2,4-dinitrophenethyl, 4-biphenethyl, 2-chloro-5-nitrobenzyl, (4-pyridylthio)ethyl, 3,3-diphenylpropyl, 2-chloro-4-nitrobenzyl, 4-dimethylaminobenzyl, 4-nitrobenzyl, 3-dimethylaminobenzyl, abietyl, 2-methyl-4-nitro-1-imidizolylpropyl, *trans*-styrylethyl, cyclopentylethyl, 2,2-dicyclohexylethyl, (2-pyridylthio)ethyl, pentadienyl, and 3-indolylethyl.

In further preferred embodiments of those described above, the R groups are those as respectively defined above and X is an oxygen atom. In other preferred embodiments, the R groups are those as respectively defined above and X is a sulfur atom. In

yet other preferred embodiments, the substituents are those as respectively defined above and R^2 is selected from the group consisting of methyl, ethyl, benzyl, allyl, and naphthylmethyl and is, even more preferably, methyl in an embodiment and benzyl in another.

In another embodiment of the above cyclic ureas and thiourea libraries and compounds, the substituents are as follows:

R^1 is methyl, benzyl, hydrogen, 2-butyl, N,N-dimethylaminobutyl, N-methylaminobutyl, 2-methylpropyl, methylsulfinylethyl, N,N-dimethylaminoethyl, N,N-dimethylaminopropyl, N',N',N'-trimethylguanidinopropyl, hydroxymethyl, 1-hydroxyethyl, 2-propyl, N-methyl-3-indolylmethyl, 4-methoxybenzyl, 4-hydroxybenzyl, propyl, butyl, cyclohexylmethyl, phenyl, 2-naphthylmethyl, or 4-imidazolylmethyl;

R^2 is methyl;

R^3 is methyl, benzyl, hydrogen, 3-hydroxypropyl, 2-butyl, N-methylaminobutyl, aminobutyl, 2-methylpropyl, methylsulfinylethyl, guanidinopropyl, hydroxymethyl, 1-hydroxyethyl, 2-propyl, N-methyl-3-indolylmethyl, 4-methoxybenzyl, 4-hydroxybenzyl, propyl, butyl, cyclohexylmethyl, phenyl, 2-naphthylmethyl, or 4-imidazolylmethyl;

R^4 is 1-phenyl-1-cyclopropylmethyl, 2-phenylbutyl, 3-phenylbutyl, *m*-tolylethyl, 3-fluorophenethyl, 3-bromophenethyl, (α,α,α-trifluoro-*m*-tolyl)ethyl, *p*-tolylethyl, 4-fluorophenethyl, 3-methoxyphenethyl, 4-bromophenethyl, 4-methoxyphenethyl, 4-ethoxyphenethyl, 4-isobutyl-α-methylphenethyl, 3,4-dichlorophenethyl, 3,5-bis(trifluoromethyl)phenethyl, 3-(3,4-

dimethoxyphenyl)propyl, 4-biphenethyl, 3-phenyl-2-methyl-2-propenyl, 3-(2-trifluoromethylphenyl)-2-propenyl, 3,4-dimethoxyphenethyl, 3,4-(dihydroxy)phenylethyl, 3-(2-methoxyphenyl)-2-propenyl, benzyl, 3-(4-chlorophenyl)-2-propenyl, *trans*-phenyl-2-propenyl, *m*-xylyl, phenethyl, 3-phenylpropyl, 4-phenylbutyl, 3,5-bis(trifluoromethyl)benzyl, butyl, heptyl, isobutyryl, (+/-)-2-methylbutyl, isovaleryl, 3-methylvaleryl, 4-methylvaleryl, 2-butenyl, 3-butenyl, *p*-xylyl, neopentyl, *tert*-butylethyl, cyclohexylmethyl, cyclohexylethyl, cyclohexylbutyl, cycloheptylmethyl, ethyl, 2-methyl-1-cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, 3-cyclopentylpropyl, cyclohexanepropyl, 4-methyl-1-cyclohexylmethyl, 4-*tert*-butyl-1-cyclohexylmethyl, 4-methylcyclohexylethyl, 2-methyl-2-butenyl, 1-adamantylethyl, 2-(α,α,α-trifluoro-*m*-toluidino)-3-pyridylmethyl, 4-nitrophenethyl, 4-(nitrophenyl)butyl, 3-(4-nitrophenyl)-2-propenyl, 2-nitrobenzyl, 2,4-dinitrophenethyl, 4-biphenethyl, 2-chloro-5-nitrobenzyl, (4-pyridylthio)ethyl, 3,3-diphenylpropyl, 2-chloro-4-nitrobenzyl, 4-dimethylaminobenzyl, 4-nitrobenzyl, 3-dimethylaminobenzyl, abietyl, 2-methyl-4-nitro-1-imidizolylpropyl, *trans*-styrylethyl, cyclopentylethyl, 2,2-dicyclohexylethyl, (2-pyridylthio)ethyl, pentadienyl, or 3-indolylethyl;

X is an oxygen atom(O) or a sulfur atom(S); and

n is one or two.

In one of the preferred embodiments of the present invention, the R groups are those as immediately defined above, when X is an oxygen atom. In yet another

preferred embodiment, the R groups are those as immediately defined above and X is a sulfur atom.

In yet further embodiments of the subject cyclic ureas and thiourea libraries and compounds, the substituents are as follows:

R^1 is methyl, benzyl, hydrogen, 2-butyl, N-methyl-N-benzylaminobutyl, N-benzylaminobutyl, 2-methylpropyl, methylsulfinylethyl, N,N-dibenzylaminoethyl, N,N-dibenzylaminopropyl, guanidinopropyl, hydroxymethyl, 1-hydroxyethyl, 2-propyl, N-benzyl-3-indolylmethyl, 4-hydroxybenzyl, propyl, butyl, cyclohexylmethyl, phenyl, 2-naphthylmethyl, or 4-imidazolylmethyl;

R^2 is benzyl;

R^3 is methyl, benzyl, hydrogen, 3-hydroxypropyl, 2-butyl, N-methylaminobutyl, aminobutyl, 2-methylpropyl, methylsulfinylethyl, guanidinopropyl, hydroxymethyl, 1-hydroxyethyl, 2-propyl, N-methyl-3-indolylmethyl, 4-methoxybenzyl, 4-hydroxybenzyl, propyl, butyl, cyclohexylmethyl, phenyl, 2-naphthylmethyl, or 4-imidazolylmethyl;

R^4 is 1-phenyl-1-cyclopropylmethyl, 2-phenylbutyl, 3-phenylbutyl, *m*-tolylethyl, 3-fluorophenethyl, 3-bromophenethyl, (α,α,α-trifluoro-*m*-tolyl)ethyl, *p*-tolylethyl, 4-fluorophenethyl, 3-methoxyphenethyl, 4-bromophenethyl, 4-methoxyphenethyl, 4-ethoxyphenethyl, 4-isobutyl-α-methylphenethyl, 3,4-dichlorophenethyl, 3,5-bis(trifluoromethyl)phenethyl, 3-(3,4-dimethoxyphenyl)propyl, 4-biphenethyl, 3-phenyl-2-methyl-2-propenyl, 3-(2-trifluoromethylphenyl)-2-propenyl, 3,4-dimethoxyphenethyl, 3,4-(dihydroxy)phenylethyl, 3-(2-methoxyphenyl)-2-propenyl, benzyl, 3-(4-chlorophenyl)-2-propenyl,

trans-phenyl-2-propenyl, *m*-xylyl, phenethyl, 3-phenylpropyl, 4-phenylbutyl, 3,5-bis(trifluoromethyl)benzyl, butyl, heptyl, isobutyryl, (+/-)-2-methylbutyl, isovaleryl, 3-methylvaleryl, 4-methylvaleryl, 2-butenyl, 3-butenyl, *p*-xylyl, neopentyl, *tert*-butylethyl, cyclohexylmethyl, cyclohexylethyl, cyclohexylbutyl, cycloheptylmethyl, ethyl, 2-methyl-1-cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, 3-cyclopentylpropyl, cyclohexanepropyl, 4-methyl-1-cyclohexylmethyl, 4-*tert*-butyl-1-cyclohexylmethyl, 4-methylcyclohexylethyl, 2-methyl-2-butenyl, 1-adamantylethyl, 2-(α,α,α-trifluoro-*m*-toluidino)-3-pyridylmethyl, 4-nitrophenethyl, 4-(nitrophenyl)butyl, 3-(4-nitrophenyl)-2-propenyl, 2-nitrobenzyl, 2,4-dinitrophenethyl, 4-biphenethyl, 2-chloro-5-nitrobenzyl, (4-pyridylthio)ethyl, 3,3-diphenylpropyl, 2-chloro-4-nitrobenzyl, 4-dimethylaminobenzyl, 4-nitrobenzyl, 3-dimethylaminobenzyl, abietyl, 2-methyl-4-nitro-1-imidizolylpropyl, *trans*-styrylethyl, cyclopentylethyl, 2,2-dicyclohexylethyl, (2-pyridylthio)ethyl, pentadienyl, or 3-indolylethyl;

X is an oxygen atom(O) or a sulfur atom(S); and

n is one or two.

In preferred embodiments of the present invention, the R groups are those as immediately defined above, when X is an oxygen atom. In yet other preferred embodiments, the R groups are those as immediately defined above and X is a sulfur atom.

In the above Formula the stereochemistry of the chiral R^1 through R^4 groups can independently be in the R or S configuration, or a mixture of the two. For

instance, as will be described in further detail below the R^1 and R^3 groups are the side chains of the α-carbon of various amino acids. The amino acids can be in the L- or D-configuration, resulting in the same R group, varying only in its stereochemistry.

In the above Formulae, the term "C_1 to C_{10} alkyl" denotes such radicals as methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, amyl, tert-amyl, hexyl, heptyl and the like. A preferred "C_1 to C_{10} alkyl" group is methyl.

The term "C_2 to C_{10} alkenyl" denotes such radicals as vinyl, allyl, 2-butenyl, 3-butenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, 2-heptenyl, 3-heptenyl, 4-heptenyl, 5-heptenyl, 6-heptenyl, as well as dienes and trienes of straight and branched chains.

The term "C_2 to C_{10} alkynyl" denotes such radicals as ethynyl, propynyl, butynyl, pentynyl, hexynyl, heptynyl, as well as di- and tri-ynes.

The term "C_1 to C_{10} substituted alkyl," "C_2 to C_{10} substituted alkenyl," and "C_2 to C_{10} substituted alkynyl," denotes that the above C_1 to C_{10} alkyl groups and C_2 to C_{10} alkenyl and alkynyl groups are substituted by one or more, and preferably one or two, halogen, hydroxy, protected hydroxy, C_3 to C_7 cycloalkyl, C_3 to C_7 substituted cycloalkyl, naphthyl, substituted naphthyl, adamantyl, abietyl, thiofuranyl, indolyl, substituted indolyl, amino, protected amino, (monosubstituted)amino, protected (monosubstituted)amino, (disubstituted)amino, guanidino, (monosubstituted)guanidino, (disubstituted)guanidino, (trisubstituted)guanidino, imidazolyl, pyrolidinyl, C_1 to C_7 acyloxy, nitro, heterocycle, substituted heterocycle, C_1 to C_4 alkyl

ester, carboxy, protected carboxy, carbamoyl, carbamoyloxy, carboxamide, protected carboxamide, cyano, methylsulfonylamino, methylsulfonyl, sulfurhydryl, C_1 to C_4 alkylthio, C_1 to C_4 alkyl sulfonyl or C_1 to C_4 alkoxy groups. The substituted alkyl groups may be substituted once or more, and preferably once or twice, with the same or with different substituents.

Examples of the above substituted alkyl groups include the cyanomethyl, nitromethyl, chloromethyl, hydroxymethyl, tetrahydropyranyloxymethyl, trityloxymethyl, propionyloxymethyl, aminomethyl, carboxymethyl, allyloxycarbonylmethyl, allylcaroxybonylaminomethyl, carbamoyloxymethyl, methoxymethyl, ethoxymethyl, t-butoxymethyl, acetoxymethyl, chloromethyl, bromomethyl, iodomethyl, 6-hydroxyhexyl, 2,4-dichloro(n-butyl), 2-amino(iso-propyl), 2-carbamoyloxyethyl chloroethyl, bromoethyl, fluoroethyl, iodoethyl, chloropropyl, bromopropyl, fluoropropyl, iodopropyl and the like.

In preferred embodiments of the subject invention, C_1 to C_{10} alkyl, C_2 to C_{10} alkenyl, C_2 to C_{10} alkynyl, C_1 to C_{10} substituted alkyl, C_2 to C_{10} substituted alkenyl, or C_2 to C_{10} substituted alkynyl preferably C_1 to C_7 , respectively, and more preferably, C_1 to C_6. However, it would be appreciated to those of skill in the art that one or a few carbons could be added to an alkyl, alkenyl, alkynyl, substituted or unsubstituted, without substantially modifying the structure and function of the subject compounds and that, therefore, such additions would not depart from the spirit of the invention.

The term "C_1 to C_4 alkoxy" as used herein denotes groups such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, t-butoxy and like groups. A preferred C_1 to C_4 alkoxy group is methoxy.

The term "C_1 to C_7 acyloxy" denotes herein groups such as formyloxy, acetoxy, propanoyloxy, butanoyloxy, pentanoyloxy, hexanoyloxy, heptanoyloxy, and the like.

Similarly, the term "C_1 to C_7 acyl" encompasses groups such as formyl, acetyl, propionoyl, butyroyl, pentanoyl, hexanoyl, heptanoyl, benzoyl and the like.

The substituent term "C_3 to C_7 cycloalkyl" includes the cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl rings. The substituent term "C_3 to C_7 substituted cycloalkyl" indicates the above cycloalkyl rings substituted by a halogen, hydroxy, protected hydroxy, phenyl, substituted phenyl, heterocycle, substituted heterocycle, C_1 to C_{10} alkyl, C_1 to C_4 alkoxy, carboxy, protected carboxy, amino, or protected amino.

The substituent term "C_3 to C_7 cycloalkenyl" indicates a 1,2, or 3-cyclopentenyl ring, a 1,2,3 or 4-cyclohexenyl ring or a 1,2,3,4 or 5-cycloheptenyl ring, while the term "substituted C_3 to C_7 cycloalkenyl" denotes the above C_3 to C_7 cycloalkenyl rings substituted by a C_1 to C_{10} alkyl radical, halogen, hydroxy, protected hydroxy, C_1 to C_4 alkoxy, carboxy, protected carboxy, amino, or protected amino.

The term "heterocyclic ring" or "heterocycle" denotes optionally substituted five-membered or six-membered rings that have 1 to 4 heteroatoms, such as oxygen, sulfur and/or nitrogen, in particular nitrogen, either alone or in conjunction with sulfur or oxygen ring atoms. These five-membered or six-membered rings may be fully unsaturated or partially unsaturated, with fully unsaturated rings being preferred. Preferred heterocyclic rings include pyridino, pyrimidino, and

pyrazino, furano, and thiofurano rings. The heterocyles can be substituted or unsubstituted as, for example, with such substituents as those described in relation to substituted phenyl or substituted naphthyl.

The term "C_7 to C_{16} phenylalkyl" denotes a C_1 to C_{10} alkyl group substituted at any position by a phenyl ring. Examples of such a group include benzyl, 2-phenylethyl, 3-phenyl-(n-prop-1-yl), 4-phenyl-(-hex-1-yl), 3-phenyl-(n-am-2-yl), 3-phenyl-(sec-butyl), and the like. A preferred group is the benzyl group.

The term "C_7 to C_{16} substituted phenylalkyl" denotes a C_7 to C_{16} arylalkyl group substituted on the C_1 to C_{10} alkyl portion with one or more, and preferably one or two, groups chosen from halogen, hydroxy, protected hydroxy, keto, C_2 to C_3 cyclic ketal, phenyl, amino, protected amino, C_1 to C_7 acyloxy, nitro, carboxy, protected carboxy, carbamoyl, carbamoyloxy, cyano, N-(methylsulfonylamino) or C_1 to C_4 alkoxy; and/or the phenyl group may be substituted with 1 or 2 groups chosen from halogen, hydroxy, protected hydroxy, nitro, C_1 to C_{10} alkyl, C_1 to C_6 substituted alkyl, C_1 to C_4 alkoxy, carboxy, protected carboxy, carboxymethyl, protected carboxymethyl, hydroxymethyl, protected hydroxymethyl, aminomethyl, protected aminomethyl, amino, (monosubstituted)amino, (disubstituted)amino, a N-(methylsulfonylamino) group, or a phenyl group, substituted or unsubstituted, for a resulting biphenyl group. When either the C_1 to C_{10} alkyl portion or the phenyl portion or both are mono- or di-substituted the substituents can be the same or different.

Examples of the term "C_7 to C_{16} substituted phenylalkyl" include groups such as 2-phenyl-1-chloroethyl, 2-(4-methoxyphenyl)eth-1-yl, 2,6-dihydroxy-4-phenyl(n-hex-2-yl), 5-cyano-3-methoxy-2-phenyl(n-pent-

3-yl), 3-(2,6-dimethylphenyl)n-prop-1-yl, 4-chloro-3-aminobenzyl, 6-(4-methoxyphenyl)-3-carboxy(n-hex-1-yl), 5-(4-aminomethyl-phenyl)-3-(aminomethyl)(n-pent-2-yl), 5-phenyl-3-keto-(n-pent-1-yl), 4-(4-aminophenyl)-4-(1,4-oxetanyl)(n-but-1-yl), and the like.

The term "C_7 to C_{16} phenylalkenyl" denotes a C_1 to C_{10} alkenyl group substituted at any position by a phenyl ring. The term "C_7 to C_{16} substituted phenylalkenyl" denotes a C_7 to C_{16} arylalkyl group substituted on the C_1 to C_{10} alkenyl portion. Substituents can the same as those as defined above in relation to C_7 to C_{16} phenylalkyl and C_7 to C_{16} substituted phenylalkyl. A preferred C_7 to C_{16} substituted phenylalkenyl is 3-(4-nitrophenyl)-2-propenyl.

The term "substituted phenyl" specifies a phenyl group substituted with one or more, and preferably one or two, moieties chosen from the groups consisting of halogen, hydroxy, protected hydroxy, cyano, nitro, C_1 to C_{10} alkyl, C_1 to C_{10} substituted alkyl, C_1 to C_4 alkoxy, carboxy, protected carboxy, carboxymethyl, protected carboxymethyl, hydroxymethyl, protected hydroxymethyl, amino, protected amino, (monosubstituted)amino, protected (monosubstituted)amino, (disubstituted)amino, trifluoromethyl, N-(methylsulfonylamino), or phenyl, substituted or unsubstituted, such that, for example, a biphenyl results.

Examples of the term "substituted phenyl" includes a mono- or di(halo)phenyl group such as 4-chlorophenyl, 2,6-dichlorophenyl, 2,5-dichlorophenyl, 3,4-dichlorophenyl, 3-chlorophenyl, 3-bromophenyl, 4-bromophenyl, 3,4-dibromophenyl, 3-chloro-4-fluorophenyl, 2-fluorophenyl and the like; a mono or di(hydroxy)phenyl groups such as 4-hydroxyphenyl, 3-hydroxyphenyl, 2,4-dihydroxyphenyl, the protected-hydroxy derivatives

thereof and the like; a nitrophenyl group such as 3-or 4-nitrophenyl; a cyanophenyl group for example, 4-cyanophenyl; a mono- or di(lower alkyl)phenyl group such as 4-methylphenyl, 2,4-dimethylphenyl, 2-methylphenyl, 4-(iso-propyl)phenyl, 4-ethylphenyl, 3-(n-prop-1-yl)phenyl and the like; a mono or di(alkoxyl)phenyl group, for example, 2,6-dimethoxyphenyl, 4-methoxyphenyl, 3-ethoxyphenyl, 4-(isopropoxy)phenyl, 4-(t-butoxy)phenyl, 3-ethoxy-4-methoxyphenyl, 3-(4-methylphenoxy)phenyl, and the like,; 3-or 4-trifluoromethylphenyl; a mono- or dicarboxyphenyl or (protected carboxy)phenyl group such as 4-carboxyphenyl or 2,4-di(protected carboxy)phenyl; a mono-or di(hydroxymethyl)phenyl or (protected hydroxymethyl)phenyl such as 3-(protected hydroxymethyl)phenyl or 3,4-di(hydroxymethyl)phenyl; a mono- or di(aminomethyl)phenyl or (protected aminomethyl)phenyl such as 2-(aminomethyl)phenyl or 2,4-(protected aminomethyl)phenyl; or a mono- or di(N-(methylsulfonylamino))phenyl such as 3-(N-(methylsulfonylamino))phenyl. Also, the term "substituted phenyl" represents disubstituted phenyl groups wherein the substituents are different, for example, 3-methyl-4-hydroxyphenyl, 3-chloro-4-hydroxyphenyl, 2-methoxy-4-bromophenyl, 4-ethyl-2-hydroxyphenyl, 3-hydroxy-4-nitrophenyl, 2-hydroxy 4-chlorophenyl and the like.

The term "substituted naphthyl" specifies a naphthyl group substituted with one or more, and preferably one or two, moieties chosen from the groups consisting of halogen, hydroxy, protected hydroxy, cyano, nitro, C_1 to C_{10} alkyl, C_1 to C_4 alkoxy, carboxy, protected carboxy, carboxymethyl, protected carboxymethyl, hydroxymethyl, protected hydroxymethyl, amino, protected amino, (monosubstituted)amino, protected (monosubstituted)amino, (disubstituted)amino trifluoromethyl or N-(methylsulfonylamino). Examples of

substituted naphthyl include 2-(methoxy)-naphthyl and 4-(methoxy)naphthyl.

The term "substituted indolyl" specifies a indolyl group substituted, either at the nitrogen or carbon, or both, with one or more, and preferably one or two, moieties chosen from the groups consisting of halogen, hydroxy, protected hydroxy, cyano, nitro, C_1 to C_{10} alkyl, C_1 to C_{10} substituted alkyl, C_1 to C_{10} alkenyl, C_7 to C_{16} phenylalkyl, C_7 to C_{16} substituted phenylalkyl, C_1 to C_6 alkoxy, carboxy, protected carboxy, carboxymethyl, protected carboxymethyl, hydroxymethyl, protected hydroxymethyl, amino, protected amino, monosubstituted amino, or disubstituted amino.

Examples of the term "substituted indolyl" includes such groups as 6-fluoro, 5-fluoro, 5-bromo, 5-hydroxy, 5-methyl, 6-methyl, 7-methyl, 1-methyl, 1-ethyl, 1-benzyl, 1-napth-2-ylmethyl, and the like. An example of a disubstituted indolyl is 1-methyl-5-methyl indolyl.

The terms "halo" and "halogen" refer to the fluoro, chloro, bromo or iodo groups.

The term "(monosubstituted)amino" refers to an amino group with one substituent chosen from the groups consisting of phenyl, substituted phenyl, C_1 to C_{10} alkyl, and C_7 to C_{16} arylalkyl, wherein the latter three substituent terms are as defined above. The (monosubstituted)amino can additionally have an amino-protecting group as encompassed by the term "protected (monosubstituted)amino."

The term "(disubstituted)amino" refers to amino groups with two substituents chosen from the group consisting of phenyl, substituted phenyl, C_1 to C_{10} alkyl, and C_7 to C_{16} arylalkyl wherein the latter three

substituent terms are as described above. The two substituents can be the same or different.

The terms "(monosubstituted)guanidino," "(disubstituted)guanidino," and "(trisubstituted)guanidino" are where the guanidino groups is substituted with one, two, or three substituents, respectively. The substituents can be any of those as defined above in relation to (monosubstituted)amino and (disubstituted)amino and, where more than one substituent is present, the substituents can be the same or different.

The term "amino-protecting group" as used herein refers to substituents of the amino group commonly employed to block or protect the amino functionality while reacting other functional groups on the amine component. The term "protected (monosubstituted)amino" means there is an amino-protecting group on the monosubstituted amino nitrogen atom. In addition, the term "protected carboxamide" means there is an amino-protecting group replacing the proton so that there is no N-alkylation. Examples of such amino-protecting groups include the formyl ("For") group, the trityl group (Trt), the phthalimido group, the trichloroacetyl group, the chloroacetyl, bromoacetyl, and iodoacetyl groups, urethane-type blocking groups, such as t-butoxy-carbonyl ("Boc"), 2-(4-biphenylyl)propyl(2)oxycarbonyl ("Bpoc"), 2-phenylpropyl(2)oxycarbonyl ("Poc"), 2-(4-xenyl)isopropoxycarbonyl, 1,1-diphenylethyl(1)-oxycarbonyl, 1,1-diphenylpropyl(1)oxycarbonyl, 2-(3,5-dimethoxyphenyl)propyl(2)oxycarbonyl ("Ddz"), 2-(p-toluyl)propyl(2)oxycarbonyl, cyclopentanyloxycarbonyl, 1-methylcyclopentanyloxycarbonyl, cyclohexanyloxy-carbonyl, 1-methylcyclohexanyloxycarbonyl, 2-methylcyclohexanyloxycarbonyl, 2-(4-toluylsulfonyl)ethoxycarbonyl,

2-(methylsulfonyl)ethoxycarbonyl, 2-(triphenylphosphino)-ethoxycarbonyl, 9-fluoroenylmethoxycarbonyl ("Fmoc"), 2-(trimethylsilyl)ethoxycarbonyl, allyloxycarbonyl, 1-(trimethylsilylmethyl)prop-1-enyloxycarbonyl, 5-benzisoxalylmethoxycarbonyl, 4-acetoxybenzyloxycarbonyl, 2,2,2-trichloroethoxycarbonyl, 2-ethynyl(2)propoxycarbonyl, cyclopropylmethoxycarbonyl, isobornyloxycarbonyl, 1-piperidyloxycarbonyl, benzyloxycarbonyl ("Z"), 4-phenylbenzyloxycarbonyl, 2-methylbenzyloxycarbonyl, α-2,4,5,-tetramethylbenzyloxycarbonyl ("Tmz"), 4-methoxybenzyloxycarbonyl, 4-fluorobenzyloxycarbonyl, 4-chlorobenzyloxycarbonyl, 3-chlorobenzyloxycarbonyl, 2-chlorobenzyloxycarbonyl, 2,4-dichlorobenzyloxycarbonyl, 4-bromobenzyloxycarbonyl, 3-bromobenzyloxycarbonyl, 4-nitrobenzyloxycarbonyl, 4-cyanobenzyloxycarbonyl, 4-(decyloxy)benzyloxycarbonyl, and the like; the benzoylmethylsulfonyl group, dithiasuccinoyl ("Dts"), the 2-(nitro)phenylsulfenyl group ("Nps"), the diphenylphosphine oxide group, and like amino-protecting groups. The species of amino-protecting group employed is not critical so long as the derivatized amino group is stable to the conditions of the subsequent reaction(s) and can be removed at the appropriate point without disrupting the remainder of the compounds. Preferred amino-protecting groups are Boc and Fmoc. Further examples of amino-protecting groups embraced to by the above term are well known in organic synthesis and the peptide art and are described by, for example, T.W. Greene and P.G.M. Wuts, "Protective Groups in Organic Synthesis," 2nd ed., John Wiley and Sons, New York, NY, 1991, Chapter 7, M. Bodanzsky, "Principles of Peptide Synthesis," 1st and 2nd revised ed., Springer-Verlag, New York, NY, 1984 and 1993, and Stewart and Young, "Solid Phase Peptide Synthesis," 2nd ed., Pierce Chemical Co., Rockford, IL, 1984, each of which is incorporated herein by reference. The related term "protected amino" defines an amino group

substituted with an amino-protecting group discussed above.

The term "carboxy-protecting group" as used herein refers to one of the ester derivatives of the carboxylic acid group commonly employed to block or protect the carboxylic acid group while reactions are carried out on other functional groups on the compound. Examples of such carboxylic acid protecting groups include 4-nitrobenzyl, 4-methoxybenzyl, 3,4-dimethoxybenzyl, 2,4-dimethoxybenzyl, 2,4,6-trimethoxybenzyl, 2,4,6-trimethylbenzyl, pentamethylbenzyl, 3,4-methylenedioxybenzyl, benzhydryl, 4,4'-dimethoxytrityl, 4,4',4"-timethoxytrityl, 2-phenylprop-2-yl, trimethylsilyl, t-butyldimethylsilyl, 2,2,2-trichloroethyl, β-(trimethylsilyl)ethyl, β-(di(n-butyl)methylsilyl)ethyl, *p*-toluenesulfonylethyl, 4-nitrobenzyl-sulfonylethyl, allyl, cinnamyl, 1-(trimethylsilylmethyl)-prop-1-en-3-yl, and like moieties. The species of carboxy-protecting group employed is not critical so long as the derivatized carboxylic acid is stable to the conditions of subsequent reaction(s) and can be removed at the appropriate point without disrupting the remainder of the molecule. Further examples of these groups are found in E. Haslam, "Protective Groups in Organic Chemistry," J.G.W. McOmie, Ed., Plenum Press, New York, NY, 1973, Chapter 5, and T.W. Greene and P.G.M. Wuts, "Protective Groups in Organic Synthesis," 2nd ed., John Wiley and Sons, New York, NY, 1991, Chapter 5, each of which is incorporated herein by reference. A related term is "protected carboxy," which refers to a carboxy group substituted with one of the above carboxy-protecting groups.

The term "hydroxy-protecting group" refers to readily cleavable groups bonded to hydroxyl groups, such as the tetrahydropyranyl, 2-methoxyprop-2-yl, 1-

ethoxyeth-1-yl, methoxymethyl, β-methoxyethoxymethyl, methylthiomethyl, t-butyl, t-amyl, trityl, 4-methoxytrityl, 4,4'-dimethoxytrityl, 4,4',4"-trimethoxytrityl, benzyl, allyl, trimethylsilyl, (t-butyl)dimethylsilyl and 2,2,2-trichloroethoxycarbonyl groups and the like. The species of hydroxy-protecting groups is not critical so long as the derivatized hydroxyl group is stable to the conditions of subsequent reaction(s) and can be removed at the appropriate point without disrupting the remainder of the cyclic urea. Further examples of hydroxy-protecting groups are described by C.B. Reese and E. Haslam, "Protective Groups in Organic Chemistry," J.G.W. McOmie, Ed., Plenum Press, New York, NY, 1973, Chapters 3 and 4, respectively, and T.W. Greene and P.G.M. Wuts, "Protective Groups in Organic Synthesis," 2nd ed., John Wiley and Sons, New York, NY, 1991, Chapters 2 and 3.

The substituent term "C_1 to C_4 alkylthio" refers to sulfide groups such as methylthio, ethylthio, n-propylthio, iso-propylthio, n-butylthio, t-butylthio and like groups.

The substituent term "C_1 to C_4 alkylsulfoxide" indicates sulfoxide groups such as methylsulfoxide, ethylsulfoxide, n-propylsulfoxide, iso-propylsulfoxide, n-butylsulfoxide, sec-butylsulfoxide, and the like.

The term "C_1 to C_4 alkylsulfonyl" encompasses groups such as methylsulfonyl, ethylsulfonyl, n-propylsulfonyl, iso-propylsulfonyl, n-butylsulfonyl, t-butylsulfonyl, and the like.

Phenylthio, phenyl sulfoxide, and phenylsulfonyl compounds are known in the art and these terms have their art recognized definition. By "substituted phenylthio," "substituted phenyl sulfoxide," and "substituted

phenylsulfonyl" is meant that the phenyl can be substituted as described above in relation to "substituted phenyl."

The substituent terms "cyclic C_2 to C_{10} alkylene," "substituted cyclic C_2 to C_{10} alkylene," "cyclic C_2 to C_{10} heteroalkylene," and "substituted cyclic C_2 to C_{10} heteroalkylene," defines such a cyclic group bonded ("fused") to the phenyl radical. The cyclic group may be saturated or contain one or two double bonds. Furthermore, the cyclic group may have one or two methylene groups replaced by one or two oxygen, nitrogen or sulfur atoms.

The cyclic alkylene or heteroalkylene group may be substituted once or twice by substituents selected from the group consisting of the following moieties: hydroxy, protected hydroxy, carboxy, protected carboxy, keto, ketal, C_1 to C_4 alkoxycarbonyl, formyl, C_2 to C_4 alkanoyl, C_1 to C_{10} alkyl, carbamoyl, C_1 to C_4 alkoxy, C_1 to C_4 alkylthio, C_1 to C_4 alkylsulfoxide, C_1 to C_4 alkylsulfonyl, halo, amino, protected amino, hydroxymethyl or a protected hydroxymethyl.

The cyclic alkylene or heteroalkylene group fused onto the benzene radical can contain two to ten ring members, but it preferably contains four to six members. Examples of such saturated cyclic groups are when the resultant bicyclic ring system is 2,3-dihydro-indanyl and a tetralin ring. When the cyclic groups are unsaturated, examples occur when the resultant bicyclic ring system is a naphthyl ring or indanyl. An example of a cyclic group which can be fused to a phenyl radical which has two oxygen atoms and which is fully saturated is dioxanyl. Examples of fused cyclic groups which each contain one oxygen atom and one or two double bonds are when the phenyl ring is fused to a furo, pyrano,

dihydrofurano, or dihydropyrano ring. Examples of cyclic groups which each have one nitrogen atom and contain one or two double more double bonds are when the phenyl is fused to a pyridino or pyrano ring. An example of a fused ring system having one nitrogen and two phenyl radicals is a carbozoyl group. Examples of cyclic groups which each have one sulfur atom and contain one or two double bonds are when the phenyl is fused to a thieno, thiopyrano, dihydrothieno or dihydrothiopyrano ring. Examples of cyclic groups which contain two heteroatoms selected from sulfur and nitrogen and one or two double bonds are when the phenyl ring is fused to a thiazolo, isothiazolo, dihydrothiazolo or dihydroisothiazolo ring. Examples of cyclic groups which contain two heteroatoms selected from oxygen and nitrogen and one or two double bonds are when the benzene ring is fused to an oxazolo, isoxazolo, dihydrooxazolo or dihydroisoxazolo ring. Examples of cyclic groups which contain two nitrogen heteroatoms and one or two double bonds occur when the benzene ring is fused to a pyrazolo, imidazolo, dihydropyrazolo or dihydroimidazolo ring.

One or more of the cylcic ureas or thioureas within a given library may be present as a pharmaceutically acceptable salt. The term "pharmaceutically-acceptable salt" encompasses those salts that form with the carboxylate anions and ammonium and include salts formed with the organic and inorganic cations discussed below. Furthermore, the term includes salts that form by standard acid-base reactions with basic groups (such as amino groups) and organic or inorganic acids. Such acids include hydrochloric, sulfuric, phosphoric, acetic, succinic, citric lactic, maleic, fumaric, palmitic, cholic, pamoic, mucic, D-glutamic, d-camphoric, glutaric, phthalic, tartaric, lauric, stearic, salicyclic, methanesulfonic,

benzenesulfonic, sorbic, picric, benzoic, cinnamic, and like acids.

The term "organic or inorganic cation" refers to counterions for the carboxylate anion of a carboxylate salt. The counter-ions are chosen from the alkali and alkaline earth metals, (such as lithium, sodium, potassium, barium and calcium); ammonium; and the organic cations (such as dibenzylammonium, benzylammonium, 2-hydroxyethylammonium, bis(2-hydroxyethyl)ammonium, phenylethylbenzylammonium, dibebenzylethylenediammonium, and like cations). Other cations encompassed by the above term include the protonated form of procaine, quinine and N-methylglucosamine, and the protonated forms of basic amino acids such as glycine, ornithine, histidine, phenylglycine, lysine and arginine. Furthermore, any zwitterionic form of the instant compounds formed by a carboxylic acid and an amino group is referred to by this term. A preferred cation for the carboxylate anion is the sodium cation.

The compounds of the above Formula can also exist as solvates and hydrates. Thus, these compounds may crystallize with, for example, waters of hydration, or one, a number of, or any fraction thereof of molecules of the mother liquor solvent. The solvates and hydrates of such compounds are included within the scope of this invention.

One or more cyclic urea or thioureas can be in the biologically active ester form, such as the non-toxic, metabolically-labile ester-form. Such ester forms induce increased blood levels and prolong the efficacy of the corresponding non-esterified forms of the compounds. Ester groups which can be used include the lower alkoxymethyl groups, for example, methoxymethyl, ethoxymethyl, iso-propoxymethyl and the like; the α-(C_1 to

C_4) alkoxyethyl groups, for example methoxyethyl, ethoxyethyl, propxyethyl, iso-propoxyethyl, and the like; the 2-oxo-1,3-diosolen-4-ylmethyl groups, such as 5-methyl-2-oxo-1,3-dioxolen-4-ylmethyl, 5-phenyl-2-oxo-1,3-dioxolen-4-ylmethyl, and the like; the C_1 to C_3 alkylthiomethyl groups, for example methylthiomethyl, ethylthiomethyl, iso-propylthiomethyl, and the like; the acyloxymethyl groups, for example pivaloyloxymethyl, pivaloyloxyethyl, α-acetoxymethyl, and the like; the ethoxycarbonyl-1-methyl group; the α-acetoxyethyl; the 3-phthalidyl or 5,6-dimethylphthalidyl groups; the 1-(C_1 to C_4 alkyloxycarbonyloxy)ethyl groups such as the 1-(ethoxycarbonyloxy)ethyl group; and the 1-(C_1 to C_4 alkylaminocarbonyloxy)ethyl groups such as the 1-(methylaminocarbonyloxy)ethyl group.

As used herein, a chemical or combinatorial "library" is an intentionally created collection of differing molecules which can be prepared by the synthetic means provided below or otherwise and screened for biological activity in a variety of formats (e.g., libraries of soluble molecules, libraries of compounds attached to resin beads, silica chips or other solid supports). The libraries can be screened in any variety of assays, such as those detailed below as well as others useful for assessing the biological activity of cyclic ureas and cyclic thioureas. The libraries will generally have at least one active compound and are generally prepared in such that the compounds are in equimolar quantities.

As will be described in further detail, four libraries were prepared, two cyclic urea libraries (X = O), one having R^2 as methyl and the other having R^2 as benzyl, and two cyclic thioureas (X = S), one having R^2 as methyl and the other having R^2 as benzyl. For these four

libraries, the R^1, R^3 and R^4 positions varied as described above and, in further detail, below. It should be appreciated, however, that such libraries can comprise several smaller "sub-libraries" or sets of mixtures of compounds, depending on the format of preparation and the varying R groups. Sublibraries are described in further detail below.

The cyclic urea and thiourea libraries and compounds of Formula **I** can be prepared according to the general Reaction Scheme **I** in Figure 1. The libraries were prepared using solid-phase techniques. The solid-phase resin, here p-methylbenzhydrylamine resin (MBHA), is indicated in Figure 1 by the large circle and dash. With reference to Reaction Scheme **I**, after the addition of a first protected amino acid (having side chain R^1) to the resin, the resin is deprotected. Following trityl deprotection, the amide linked to the solid support is selectively N-alkylated (illustrated in Figure 1). The N-alkylation can be performed using lithium t-butoxide in THF, followed by addition of the alkylating agent in DMSO. The alkylating agents are those which include the R^2 groups described above, derivatived with, for example, a bromo, iodo, triflate or methylsulfonate group. Other alkylating derivatives of the group R^2 are well known. Preferably the alkylating agent is methyl iodide or benzyl bromide. This method of N-alkylation is known and has been used for the synthesis of soluble peptidomimetic combinatorial libraries through successive or exhaustive amide alkylation as described, for example, in Dorner et al. Bioorg. & Med. Chem., 4:709 (1996) and Ostresh et al. Proc. Nat. Acad. Sci., 91:11138 (1994), both of which are incorporated herein by reference.

Again with reference to Reaction Scheme **I** in Figure 1, after N-alkylation, the Trt protecting group is

removed with 2% TFA in DCM and a second protected amino acid (having side chain R^3) is added using traditional solid phase peptide chemistry. Following deprotection, the resulting dipeptide is then acylated with one of a wide range of available carboxylic acids to obtain the acylated dipeptide. Exemplary amino acid and carboxylic acids are discussed in detail below.

The next key step in the synthetic process, as shown in Figure 1, is the reduction of the amide groups of the acylated dipeptide using diborane in THF at 65°C to generate a tertiary and two secondary amines. This method has been used to generate diverse chemical libraries using the "libraries from libraries" concept as described, for instance, in Ostresh et al. Proc. Nat. Acad. Sci., 91:11138 (1994) and Cuervo et al. *In Peptides, 1994*, Proceedings of the 23rd European Peptide Symposium (Maia,H.L.S, ed): 465-466 (1995), each of which are incorporated herein by reference. The cyclizations to obtain the five-member ring (and six-member ring when R^3 is β-Ala and, therefore, n is two) cyclic ureas and cyclic thioureas were performed using carbonyldiimidazole and thiocarbonyldiimidazole as described in the ensuing Example. Alternatively, the cyclization step can carried out using phosgene, triphosgene or thiophosgene by the procedures described, for example, in Majer and Randad, J.Org.Chem.,59:1937-1938 (1994), and Kim et al., Tetrahedron Lett., 37:5309 (1996), both of which are incorporated herein by reference.

Any variety of amino acids can be used with the present invention as described above to generate a vast array of cyclic ureas and thioureas with different R^1 and R^3 groups. As described in the ensuing Example, forty different first amino acids were coupled to the resin, which amino acids contain R^1. The forty amino acids included Ala, Phe, Gly, Ile, Lys(Boc), Leu, Met(O), Asn,

Gln, Arg(Pmc), Ser(tBu), Thr(tBu), Val, Trp, Tyr(Brz), Tyr(tBu), ala, phe, ile, lys(Boc), leu, asn, gln, ser, thr(tBu), val, trp, tyr(tBu), arg(Pmc), Nle, nle, Nva, nva, Nap, nap, Phg, Cha, cha, His(Trt) and his(Trt). After the above described N-alkylation, thirty seven different second amino acids were coupled, thereby providing thirty seven various R^3 groups. Those thirty seven amino acids included Ala, Phe, Gly, Ile, Leu, Met(O), Arg(Pmc), Ser(tBu), Thr(tBu),Val, Trp(Boc), Tyr(Brz), Tyr(tBu), ala, phe, ile, leu, ser, thr(tBu), val, trp(Boc), tyr(tBu), arg(Pmc), Nle, nle, Nva, nva, Nap, nap, Phg, Glu(tBu), glu(tBu), β-Ala, Cha, cha, His(Trt) and his(Trt).

As used herein, abbreviations for the various amnio acid side-chain protecting groups are as follows: "Trt" for trityl, "tBu" for *tert*-butyl, "Boc" for *tert*-butoxycarbonyl, "Brz" for 2-bromobenzyloxycarbonyl, and "Pmc" for 2,2,5,7,8-pentamethylchroman-6-sulfonyl. These abbreviations and any others used herein are those which are commonly known and used in the field. Moreover, also as is commonly practiced in the field and with reference to the amino acid nomenclature, all lower case lettering herein means the D-form of the amino acid as opposed to the L-form. Other nomenclature and three-letter abbreviations used herein for amino acids and derivatives thereof, as well as their respective side chains are as follows:

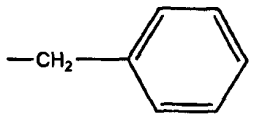
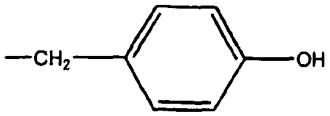
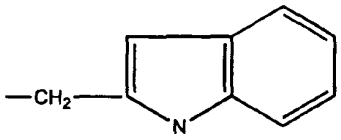
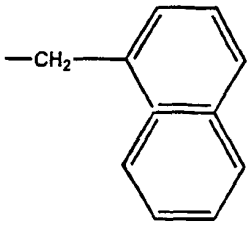
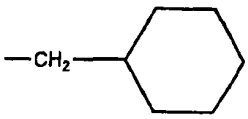
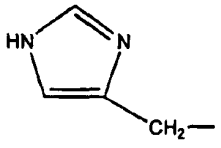
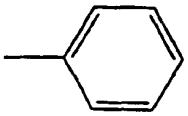
TABLE 1		
AMINO ACID NAME		SIDE CHAIN R
FULL	3-LETTER CODE	(FOR R^1 AND R^3)
Glycine	Gly	-H
Alanine	Ala	$-CH_3$
Valine	Val	$-CH(CH_3)_2$
Leucine	Leu	$-CH_2CH(CH_3)_2$
Isoleucine	Ile	$-CH(CH_3)CH_2CH_3$
Lysine	Lys	$-(CH_2)_4NH_2$
Arginine	Arg	$-CH_2CH_2CH_2NHC(NH)NH_2$
Glutamic Acid	Glu	$-CH_2CH_2COOH$
Serine	Ser	$-CH_2OH$
Threonine	Thr	$-CH(OH)CH_3$
Phenylalanine		
Tyrosine	Tyr	
Tryptophan	Trp	
β-Alanine	β-Ala	$-CH_2-CH_2-$
Norvaline	Nva	$-CH_2CH_2CH_3$
Norleucine	Nle	$-CH_2CH_2CH_2CH_3$
Napthylalanine	Nap	

TABLE 1		
AMINO ACID NAME		SIDE CHAIN R
FULL	3-LETTER CODE	(FOR R^1 AND R^3)
Cyclohexylalanine	Cha	
Methionine	Met	$-CH_2CH_2-S-CH_3$
Asparagine	Asn	$-CH_2C(O)NH_2$
Glutamine	Gln	$-CH_2CH_2C(O)NH_2$
Histidine	His	
Phenylglycine	Phg	

As can be seen from the side chains exemplified in the above Table, n in Formula I in all preferred instances is 1, the α-carbon, except when β-Alanine is used, in which case n is 2 and the core ring of the urea will be enlarged to a six-membered ring.

It should be appreciated from the above-described embodiments of R^1 and R^3, as well as from the described reaction scheme, that some of the amino acid side chains are modified during the synthesis. For instance some of the R^1 amino acid side chains are modified by the N-alkylation and/or the reduction steps. Similarly, certain R^3 groups are modified by the reduction procedures. Accordingly, with reference to the forty preferred embodiments of R^1 and the thirty seven of R^3, they are described above and below, except in Table I, in their modified form. A specific example of a modified lysine side chain is provided in Example II below.

As well, a variety of carboxylic acids can be used in the acylation step of Reaction Scheme I, thereby generating a wide array of substituents at the R^4 position of the cyclic ureas and thioureas. Preferably, eighty carboxylic acids were used in preparing the subject libraries and compounds. Those eighty carboxylic acids were 1-phenyl-1-cyclopropanecarboxylic acid, 2-phenylbutyric acid, 3-phenylbutyric acid, *m*-tolylacetic acid, 3-fluorophenylacetic acid, 3-bromophenylacetic acid, (α,α,α-trifluoro-*m*-tolyl)acetic acid, *p*-tolylacetic acid, 4-fluorophenylacetic acid, 3-methoxyphenylacetic acid, 4-bromophenylacetic acid, 4-methoxyphenylacetic acid, 4-ethoxyphenylacetic acid, 4-isobutyl-α-methylphenylacetic acid, 3,4-dichlorophenylacetic acid, 3,5-bis(trifluoromethyl)phenylacetic acid, 3-(3,4-dimethoxyphenyl)propionic acid, 4-biphenylacetic acid, α-methylcinnamic acid, 2-(trifluoromethyl)cinnamic acid, (3,4-dimethoxyphenyl)acetic acid, 3,4-(methylenedioxy)phenylacetic acid, 2-methoxycinnamic acid, benzoic acid, 4-chlorocinnamic acid, *trans*-cinnamic acid, *m*-toluic acid, phenylacetic acid, hydrocinnamic acid, 4-phenylbutyric acid, 3,5-bis(trifluoromethyl)benzoic acid, butyric acid, heptanoic acid, isobutyric acid, (+/-)-2-methylbutyric acid, isovaleric acid, 3-methylvaleric acid, 4-methylvaleric acid, crotonic acid, vinylacetic acid, *p*-toluic acid, trimethylacetic acid, *tert*-butylacetic acid, cyclohexanecarboxylic acid, cyclohexylacetic acid, cyclohexanebutyric acid, cycloheptanecarboxylic acid, acetic acid, 2-methylcyclopropanecarboxylic acid, cyclobutanecarboxylic acid, cyclopentanecarboxylic acid, 3-cyclopentylpropionic acid, cyclohexanepropionic acid, 4-methyl-1-cyclohexanecarboxylic acid, 4-*tert*-butyl-cyclohexanecarboxylic acid, 4-methylcyclohexaneacetic acid, tiglic acid, 1-adamantaneacetic acid, niflumic acid, 4-nitrophenylacetic acid, 4-(nitrophenyl)butyric

acid, 4-nitrocinnamic acid, 2-nitrobenzoic acid, 2,4-dinitrophenylacetic acid, 4-biphenylacetic acid, 2-chloro-5-nitrobenzoic acid, (4-pyridilthio)acetic acid, 3-3- diphenylpropionic acid, 2-chloro-4-nitrobenzoic acid, 4-dimethylaminobenzoic acid, 4-nitrobenzoic acid, 3-dimethylbenzoic acid, abietic acid, 2-methyl-4-nitro-1-imidizolepropionic acid, *trans*-styrylacetic acid, cyclopentylacetic acid, dicyclohexylacetic acid, (2-pyridithio)acetic acid, pentadienoicacid, and indole-3-acetic acid.

The nonsupport-bound library mixtures were screened in solution in radio-receptor inhibition assays and an anti-bacterial assay described in detail below. Deconvolution of highly active mixtures can then be carried out by iterative, or positional scanning methods. These techniques, the iterative approach or the positional scanning approach, can be utilized for finding other active compounds within the libraries of the present invention using any one of the below-described assays or others well known in the art.

The iterative approach is well-known and is set forth in general in Houghten *et al.*, Nature, 354, 84-86 (1991) and Dooley *et al.*, Science, 266, 2019-2022 (1994), both of which are incorporated herein by reference. In the iterative approach, for example, sub-libraries of a molecule having three variable groups are made wherein the first variable is defined. Each of the compounds with the defined variable group is reacted with all of the other possibilities at the other two variable groups. These sub-libraries are each tested to define the identity of the second variable in the sub-library having the highest activity in the screen of choice. A new sub-library with the first two variable positions defined is reacted again with all the other possibilities at the

remaining undefined variable position. As before, the identity of the third variable position in the sub-library having the highest activity is determined. If more variables exist, this process is repeated for all variables, yielding the compound with each variable contributing to the highest desired activity in the screening process. Promising compounds from this process can then be synthesized on larger scale in traditional single-compound synthetic methods for further biological investigation.

The positional-scanning approach has been described for various libraries as described, for example, in R. Houghten *et al.* PCT/US91/08694 and U.S. Patent 5,556,762, both of which are incorporated herein by reference. The positional scanning approach is used as described below in the preparation and screening of the libraries. In the positional scanning approach sublibraries are made defining only one variable with each set of sublibraries- and all possible sublibraries with each single variable defined (and all other possibilities at all of the other variable positions) is made and tested. From the instant description one skilled in the art could synthesize libraries wherein 2 fixed positions are defined at a time. From the testing of each single-variable defined library, the optimum substituent at that position is determined, pointing to the optimum or at least a series of compounds having a maximum of the desired biological activity. Thus, the number of sublibraries for compounds with a single position defined will be the number of different substituents desired at that position, and the number of all the compounds in each sublibrary will be the product of the number of substituents at each of the other variables.

Individual compounds and pharmaceutical compositions containing the new cyclic ureas and thioureas, as well as methods of using the same are included within the scope of the present invention. The new urea compounds of the present invention can be used for a variety of purposes and indications and as medicaments for any such purposes and indications. For example, cyclic urea moieties are found in many biologically active compounds and, as described above, have even been used as potent inhibitors of HIV protease and HIV replication.

Moreover, as shown in Example IV, cyclic thioureas of the present invention have antimicrobial activity. Thus the ureas of the present invention can be used to treat infections. The ability of the compounds to inhibit bacterial growth can be determined by methods well known in the art. An exemplary *in vitro* antimicrobial activity assay is described in Blondelle and Houghten, Biochemistry 30:4671-4678 (1991), which is incorporated herein by reference. In brief, *Staphylococcus aureus* ATCC 29213 (Rockville, MD) is grown overnight at 37°C in Mueller-Hinton broth, then re-inoculated and incubated at 37°C to reach the exponential phase of bacterial growth (i.e., a final bacterial suspension containing 10^5 to 5 x 10^5 colony-forming units/ml). The concentration of cells is established by plating 100 µl of the culture solution using serial dilutions (e.g., 10^{-2}, 10^{-3} and 10^{-4}) onto solid agar plates. In 96-well tissue culture plates cyclic ureas, individual or in mixtures, are added to the bacterial suspension at concentrations derived from serial two-fold dilutions ranging from 1500 to 2.9 µg/ml. The plates are incubated overnight at 37°C and the growth determined at each concentration by OD_{620} nm. The IC_{50} (the

concentration necessary to inhibit 50% of the growth of the bacteria) can then be calculated.

Additional assays can be, and have been, used to test the biological activity of the instant ureas. Such assays include a competitive enzyme-linked immunoabsorbent assay and, as described in Example IV, radio-receptor assays. The latter test, the radio-receptor assay, can be selective for any one of the μ, κ, or δ opiate receptors and is, therefore, an indication of ureas' analgesic properties as described, for example, in Dooley et al., Proc. Natl. Acad. Sci., 90:10811-10815 (1993). Additionally, such compounds can be tested in a σ receptor assay. Ligands for the σ receptor can be useful as antipsychotic agents, as described in Abou-Gharbia et al., Annual Reports in Medicinal Chemistry, 28:1-10 (1993).

Competitive Enzyme-Linked Immunosorbent Assay (ELISA): The competitive ELISA method which can be used here is a modification of the direct ELISA technique described previously in Appel et al., J. Immunol. 144:976-983 (1990), which is incorporated herein by reference. It differs only in the MAb addition step. Briefly, multi-well microplates are coated with the antigenic peptide (Ac-GASPYPNLSNQQT-NH_2) at a concentration of 100 pmol/50 μl. After blocking, 25 μl of a 1.0 mg/ml solution of each urea mixture of a synthetic combinatorial library (or individual urea) is added, followed by MAb 125-10F3 (Appel et al., *supra*) (25 μl per well). The MAb is added at a fixed dilution in which the urea in solution effectively competes for MAb binding with the antigenic peptide adsorbed to the plate. The remaining steps are the same as for direct ELISA. The concentration of urea necessary to inhibit 50% of the MAb binding to the control peptide on the plate (IC_{50}) is determined by serial dilutions of the cyclic urea.

Radio-Receptor Assay: Particulate membranes can be prepared using a modification of the method described in Pasternak et al., Mol. Pharmacol. 11:340-351 (1975), which is incorporated herein by reference. Rat brains frozen in liquid nitrogen can be obtained from Rockland (Gilbertsville, PA). The brains are thawed, the cerebella removed and the remaining tissue weighed. Each brain is individually homogenized in 40 ml Tris-HCl buffer (50 mM, pH 7.4, 4°C) and centrifuged (Sorvall® RC5C SA-600: Du Pont, Wilmington, DE) (16,000 rpm) for 10 mins. The pellets are resuspended in fresh Tris-HCl buffer and incubated at 37°C for 40 mins. Following incubation, the suspensions are centrifuged as before, the resulting pellets resuspended in 100 volumes of Tris buffer and the suspensions combined. Membrane suspensions are prepared and used in the same day. Protein content of the crude homogenates generally range from 0.15-0.2 mg/ml as determined using the method described in M.M. Bradford, M.M., Anal. Biochem. 72:248-254 (1976), which is incorporated herein by reference.

Binding assays are carried out in polypropylene tubes, each tube containing 0.5 ml of membrane suspension. 8 nM of ^{3}H-[D-Ala^{2},Me-Phe^{4},Gly-ol^{5}]enkephalin (DAMGO) (specific activity = 36 Ci/mmol, 160,000 cpm per tube; which can be obtained from Multiple Peptide Systems, San Diego, CA, through NIDA drug distribution program 271-90-7302) and 80 μg/ml of urea, individual or as a mixture and Tris-HCl buffer in a total volume of 0.65 ml. Assay tubes are incubated for 60 mins. at 25°C. The reaction is terminated by filtration through GF-B filters on a Tomtec harvester (Orange, CT). The filters are subsequently washed with 6 ml of Tris-HCl buffer, 4°C. Bound radioactivity is counted on a Pharmacia Biotech Betaplate Liquid Scintillation Counter (Piscataway, NJ) and expressed in cpm. To determine inter- and intra-assay variation, standard curves in

which ^{3}H-DAMGO is incubated in the presence of a range of concentrations of unlabeled DAMGO (0.13-3900 nM) are generally included in each plate of each assay (a 96-well format). Competitive inhibition assays are performed as above using serial dilutions of the ureas, individually or in mixtures. IC_{50} values (the concentration necessary to inhibit 50% of ^{3}H-DAMGO binding) are then calculated. As opposed to this μ receptor selective assay, assays selective for κ receptors can be carried out using [^{3}H]-U69,593 (3 nM, specific activity 62 Ci/mmol) as radioligand. Assays selective for δ opiate receptors can be carried out using tritiated DSLET ([D-Ser^2, D-Leu^5]-threonine-enkephalin) as radioligand. Similarly, assays for the σ receptor assay are the same as the μ assay but use radiolabeled pentazocine as ligand.

As pharmaceutical compositions for treating infections, pain, or other indications known to be treatable by cyclic ureas or thioureas, the urea compounds of the present invention are generally in a pharmaceutical composition so as to be administered to a subject at dosage levels of from 0.7 to 7000 mg per day, and preferably 1 to 500 mg per day, for a normal human adult of approximately 70 kg of body weight, this translates into a dosage of from 0.01 to 100 mg/kg of body weight per day. The specific dosages employed, however, can be varied depending upon the requirements of the patient, the severity of the condition being treated, and the activity of the compound being employed. The determination of optimum dosages for a particular situation is within the skill of the art.

For preparing pharmaceutical compositions containing compounds of the invention, inert, pharmaceutically acceptable carriers are used. The pharmaceutical carrier can be either solid or liquid. Solid form preparations include, for example, powders,

tablets, dispersible granules, capsules, cachets, and suppositories.

A solid carrier can be one or more substances which can also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, or tablet disintegrating agents; it can also be an encapsulating material.

In powders, the carrier is generally a finely divided solid which is in a mixture with the finely divided active component. In tablets, the active compound is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

For preparing pharmaceutical composition in the form of suppositories, a low-melting wax such as a mixture of fatty acid glycerides and cocoa butter is first melted and the active ingredient is dispersed therein by, for example, stirring. The molten homogeneous mixture is then poured into convenient-sized molds and allowed to cool and solidify.

Powders and tablets preferably contain between about 5% to about 70% by weight of the active ingredient. Suitable carriers include, for example, magnesium carbonate, magnesium stearate, talc, lactose, sugar, pectin, dextrin, starch, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, a low-melting wax, cocoa butter and the like.

The pharmaceutical compositions can include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component (with or without other carriers) is

surrounded by a carrier, which is thus in association with it. In a similar manner, cachets are also included.

Tablets, powders, cachets, and capsules can be used as solid dosage forms suitable for oral administration.

Liquid pharmaceutical compositions include, for example, solutions suitable for oral or parenteral administration, or suspensions, and emulsions suitable for oral administration. Sterile water solutions of the active component or sterile solutions of the active component in solvents comprising water, ethanol, or propylene glycol are examples of liquid compositions suitable for parenteral administration.

Sterile solutions can be prepared by dissolving the active component in the desired solvent system, and then passing the resulting solution through a membrane filter to sterilize it or, alternatively, by dissolving the sterile compound in a previously sterilized solvent under sterile conditions.

Aqueous solutions for oral administration can be prepared by dissolving the active compound in water and adding suitable flavorants, coloring agents, stabilizers, and thickening agents as desired. Aqueous suspensions for oral use can be made by dispersing the finely divided active component in water together with a viscous material such as natural or synthetic gums, resins, methyl cellulose, sodium carboxymethyl cellulose, and other suspending agents known to the pharmaceutical formulation art.

Preferably, the pharmaceutical composition is in unit dosage form. In such form, the composition is divided into unit doses containing appropriate quantities

of the active urea. The unit dosage form can be a packaged preparation, the package containing discrete quantities of the preparation, for example, packeted tablets, capsules, and powders in vials or ampules. The unit dosage form can also be a capsule, cachet, or tablet itself, or it can be the appropriate number of any of these packaged forms.

The following Examples are intended to illustrate but not limit the present invention.

EXAMPLE I

This example provides the synthesis of four combinatorial libraries of the present invention; (1) X = O, R^2 = methyl, (2) X = O, R^2 = benzyl, (3) X = S, R^2 = methyl and (4) X = S, R^2 = benzyl. The R^1, R^3 and R^4 groups varied as described above and below. Again, forty first amino acids were used, generating at least forty R^1 groups, depending on the modifications to the side chains. The amino acids used to generate R^1 are again listed below in Table 2. Thirty-seven second amino acids were used to generate the various R^3 groups, which amino acids are also again summarized in Table 2 below. Finally the eighty carboxylic acids used to acylate the dipeptides and generate R^4 are also listed again in Table 2. Therefore, Table 2 provides a summary of all the amino acids (R^1 and R^3), alkylation moieties (R^2) and carboxylic acid components (R^4) used in the preparation of the libraries.

TABLE 2

SUMMARY OF R GROUPS IN PREPARED LIBRARIES

	R^1	R^2	R^3	R^4
1	Ala	Me	Ala	1-phenyl-1-cyclopropane-carboxylic acid

TABLE 2

SUMMARY OF R GROUPS IN PREPARED LIBRARIES

	R^1	R^2	R^3	R^4
2	Phe	Bzl	Phe	2-phenylbutyric acid
3	Gly		Gly	3-phenylbutyric acid
4	Ile		Ile	*m*-tolylacetic acid
5	Lys (Boc)		Leu	3-fluorophenylacetic acid
6	Leu		Met(O)	3-bromophenylacetic acid
7	Met(O)		Arg (Pmc)	(α,α,α-trifluoro-*m*-tolyl) acetic acid
8	Asn		Ser (tBu)	*p*-tolylacetic acid
9	Gln		Thr (tBu)	4-fluorophenylacetic acid
10	Arg (Pmc)		Val	3-methoxyphenylacetic acid
11	Ser (tBu)		Trp (Boc)	4-bromophenylacetic acid
12	Thr (tBu)		Tyr (Brz)	4-methoxyphenylacetic acid
13	Val		Tyr (tBu)	4-ethoxyphenylacetic acid
14	Trp		ala*	4-isobutyl-α-methylphenylacetic acid
15	Tyr (Brz)		phe	3,4-dichlorophenylacetic acid
16	Tyr (tBu)		ile	3,5-bis(trifluoromethyl) phenylacetic acid
17	ala		leu	3-(3,4-dimethoxyphenyl)-propionic acid
18	phe		ser	4-biphenylacetic acid
19	ile		thr (tBu)	α-methylcinnamic acid
20	lys (Boc)		val	2-(trifluoromethyl)cinnamic acid
21	leu		trp (Boc)	(3,4-dimethoxyphenyl)acetic acid

TABLE 2

SUMMARY OF R GROUPS IN PREPARED LIBRARIES

	R^1	R^2	R^3	R^4
22	asn		try (tBu)	3,4-(methylenedioxy)-phenylacetic acid
23	gln		arg (Pmc)	2-methoxycinnamic acid
24	ser		Nle	benzoic acid
25	thr (tBu)		nle	4-chlorocinnamic acid
26	val		Nva	*trans*-cinnamic acid
27	trp		nva	*m*-toluic acid
28	tyr (tBu)		Nap	phenylacetic acid
29	arg (Pmc)		nap	hydrocinnamic acid
30	Nle		Phg	4-phenylbutyric acid
31	nle		Glu (tBu)	3,5-bis(trifluoromethyl)-benzoic acid
32	Nva		glu (tBu)	butyric acid
33	nva		βAla	heptanoic acid
34	Nap		Cha	isobutyric acid
35	nap		cha	(+/-)-2-methylbutyric acid
36	Phg		His (Trt)	isovaleric acid
37	Cha		his (Trt)	3-methylvaleric acid
38	cha			4-methylvaleric acid
39	His (Trt)			crotonic acid
40	his (Trt)			vinylacetic acid
41				*p*-toluic acid
42				trimethylacetic acid
43				*tert*-butylacetic acid

TABLE 2

SUMMARY OF R GROUPS IN PREPARED LIBRARIES

	R^1	R^2	R^3	R^4
44				cyclohexanecarboxylic acid
45				cyclohexylacetic acid
46				cyclohexanebutyric acid
47				cycloheptanecarboxylic acid
48				acetic acid
49				2-methylcyclopropane-carboxylic acid
50				cyclobutanecarboxylic acid
51				cyclopentanecarboxylic acid
52				3-cyclopentylpropionic acid
53				cyclohexanepropionic acid
54				4-methyl-1-cyclohexanecarboxylic acid
55				4-tert-butylcyclohexanecarboxylic acid
56				4-methylcyclohexaneacetic acid
57				tiglic acid
58				1-adamantaneacetic acid
59				niflumic acid
60				4-nitrophenyl acetic acid
61				4-(nitrophenyl)butyric acid
62				4-nitrocinnamic acid
63				2-nitrobenzoic acid
64				2,4-dinitrophenyl acetic acid
65				4-biphenyl acetic acid
66				2-chloro-5-nitrobenzoic acid
67				(4-pyridylthio)acetic acid
68				3-3 diphenyl propionic acid

TABLE 2

SUMMARY OF R GROUPS IN PREPARED LIBRARIES

	R^1	R^2	R^3	R^4
69				2-chloro-4-nitrobenzoic acid
70				4-dimethylaminobenzoic acid
71				4-nitrobenzoic acid
72				3-dimethylaminobenzoic acid
73				abietic acid
74				2-methyl-4-nitro-1-imidizole propionic acid
75				*trans*-styryl acetic acid
76				cyclopentyl acetic acid
77				dicyclohexyl acetic acid
78				(2-pyridylthio)acetic acid
79				pentadienoic acid
80				indole-3-acetic acid

*lower case lettering indicates D-amino acids

Pools of libraries were prepared in the positional scan format. A typical procedure for the combinatorial synthesis of the subject cyclic ureas and cyclic thioureas libraries was as follows. One hundred and eighty mg of p-methylbenzhydrylamine (MBHA) resin (0.81 meq/g, 100-200 mesh) was contained within a sealed polypropylene mesh packet. Reactions were carried out in a 10 ml polyethylene bottle. Following neutralization with 5% diisopropylethylamine (DIEA) in dichloromethane (DCM), the resin was washed with DCM. The first amino acid (Fmoc-Xaa-OH in Figure 1) was coupled using the conventional reagents hydroxybenzotriazole (HOBt) and diisopropylcarbodiimide (DICI). Following removal of the protecting group with 25% piperidine in DMF, the mesh packet was shaken overnight in a solution of trityl chloride in DCM/DMF (9:1) in the presence of DIEA. Completeness of the trityl coupling was verified using

the bromophenol blue color test as described in (Krchnak et al. Coll. Czech. Chem. Commun., 53:2542 (1988), which is incorporated herein by reference.

N-alkylation was then performed by treatment of the resin packet with 1 M lithium t-butoxide in THF. Excess base was removed by cannulation, followed by addition of the individual alkylating agent in DMSO. The solution was vigorously shaken for 2 h at room temperature. Upon removal of the trityl group with 2% TFA in DCM (2 x 10 min), the packet was washed, neutralized and the second amino acid (Fmoc-Xaa-OH in Figure 1) coupled. Following removal of the Fmoc group, the dipeptide was individually acylated with a carboxylic acid in the presence of diisopropylcarbodiimide (DICI) and 1-hydroxybenzotriazole (HOBt).

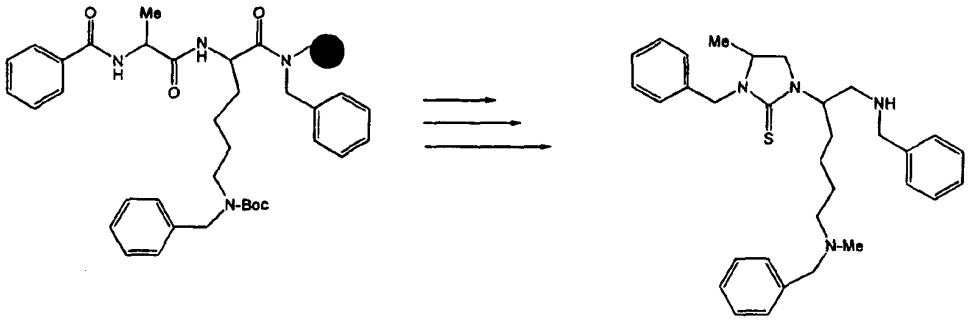
The reductions were performed in 50 ml kimax tubes under nitrogen. Boric acid (40x) and trimethyl borate (40x) were added, followed by 1M BH_3-THF (40x). The tubes were heated at 65°C for 72 h, followed by quenching with MeOH. The resin was then washed with tetrahydrofuran and methanol. The amine-borane complex was disassociated by overnight treatment with piperdine at 65°C.

The cyclization occurred following treatment of the reduced acylated dipeptide overnight with carbonyldiimidazole (0.5 M in dichloromethane anhydrous) for cyclic urea formation and thiocarbonyldiimidazole (0.5 M in dichloromethane anhydrous) for thiourea formation. Following cleavage from the resin with anhydrous HF by the procedures of Houghten et al. Int. J. Pep. Prot. Res., 27:673 (1986), which is incorporated herein by reference, in the presence of anisole, the desired products were extracted and lyophilized. The

desired products were obtained in good yields and high purity (>90% by HPLC) following lyophilization.

EXAMPLE II

Figure 2 provides the RP-HPLC and LCQ-Mass spectra of the cyclic urea (X = O) (expected mass: 498) and cyclic thiourea (X = S) (expected mass: 514), with: R^2 = Bzl, R^1 = modified side chain of lysine, R^3 = side chain of alanine, R^4 = benzyl (benzoic acid before reduction) and n = one. This thiourea, and its modified lysine side chain are provided below.



EXAMPLE III

Following the procedures of Example I, the following pools of libraries containing N-benzyl aminocyclic thioureas were prepared by the positional scan format. Therefore, X = S and R^2 = benzyl and the remaining R groups and their respective pool reference numbers are identified in Table 3 below. Each of the 157 pools were screened in an anti-microbial assay and μ and κ-opioid receptor assays as provided in Example IV. This Example and Table 3 is provided for further reference for

pool compositions in relation to the biological data in the ensuing Example.

TABLE 3

LIBRARY POOL REFERENCE NUMBERS AND VARIABLE R GROUPS FOR N-BENZYL AMINOCYCLIC THIOUREA LIBRARY

Pool No.	R^1	R^3	R^4
1	X	X	1-phenyl-1-cyclopropanecarboxylic acid
2	X	X	2-phenylbutyric acid
3	X	X	3-phenylbutyric acid
4	X	X	*m*-tolylacetic acid
5	X	X	3-fluorophenylacetic acid
6	X	X	3-bromophenylacetic acid
7	X	X	(α,α,α-trifluoro-*m*-tolyl) acetic acid
8	X	X	*p*-tolylacetic acid
9	X	X	4-fluorophenylacetic acid
10	X	X	3-methoxyphenylacetic acid
11	X	X	4-bromophenylacetic acid
12	X	X	4-methoxyphenylacetic acid
13	X	X	4-ethoxyphenylacetic acid
14	X	X	4-isobutyl-α-methylphenylacetic acid
15	X	X	3,4-dichlorophenylacetic acid
16	X	X	3,5-bis(trifluoromethyl) phenylacetic acid
17	X	X	3-(3,4-dimethoxyphenyl)propionic acid
18	X	X	4-biphenylacetic acid
19	X	X	α-methylcinnamic acid
20	X	X	2-(trifluoromethyl)cinnamic acid
21	X	X	(3,4-dimethoxyphenyl)acetic acid

TABLE 3

LIBRARY POOL REFERENCE NUMBERS AND VARIABLE R GROUPS FOR N-BENZYL AMINOCYCLIC THIOUREA LIBRARY

Pool No.	R^1	R^3	R^4
22	X	X	3,4-(methylenedioxy)phenylacetic acid
23	X	X	2-methoxycinnamic acid
24	X	X	benzoic acid
25	X	X	4-chlorocinnamic acid
26	X	X	*trans*-cinnamic acid
27	X	X	*m*-toluic acid
28	X	X	phenylacetic acid
29	X	X	hydrocinnamic acid
30	X	X	4-phenylbutyric acid
31	X	X	3,5-bis(trifluoromethyl)benzoic acid
32	X	X	butyric acid
33	X	X	heptanoic acid
34	X	X	isobutyric acid
35	X	X	(+/-)-2-methylbutyric acid
36	X	X	isovaleric acid
37	X	X	3-methylvaleric acid
38	X	X	4-methylvaleric acid
39	X	X	crotonic acid
40	X	X	vinylacetic acid
41	X	X	*p*-toluic acid
42	X	X	trimethylacetic acid
43	X	X	*tert*-butylacetic acid
44	X	X	cyclohexanecarboxylic acid
45	X	X	cyclohexylacetic acid

TABLE 3

LIBRARY POOL REFERENCE NUMBERS AND VARIABLE R GROUPS FOR N-BENZYL AMINOCYCLIC THIOUREA LIBRARY

Pool No.	R^1	R^3	R^4
46	X	X	cyclohexanebutyric acid
47	X	X	cycloheptanecarboxylic acid
48	X	X	acetic acid
49	X	X	2-methylcyclopropanecarboxylic acid
50	X	X	cyclobutanecarboxylic acid
51	X	X	cyclopentanecarboxylic acid
52	X	X	3-cyclopentylpropionic acid
53	X	X	cyclohexanepropionic acid
54	X	X	4-methyl-1-cyclohexanecarboxylic acid
55	X	X	4-tert-butylcyclohexanecarboxylic acid
56	X	X	4-methylcyclohexaneacetic acid
57	X	X	tiglic acid
58	X	X	1-adamantaneacetic acid
59	X	X	niflumic acid
60	X	X	4-nitrophenyl acetic acid
61	X	X	4-(nitrophenyl)butyric acid
62	X	X	4-nitrocinnamic acid
63	X	X	2-nitrobenzoic acid
64	X	X	2,4-dinitrophenyl acetic acid
65	X	X	4-biphenyl acetic acid
66	X	X	2-chloro-5-nitrobenzoic acid
67	X	X	(4-pyridylthio)acetic acid
68	X	X	3-3 diphenyl propionic acid
69	X	X	2-chloro-4-nitrobenzoic acid

TABLE 3

LIBRARY POOL REFERENCE NUMBERS AND VARIABLE R GROUPS FOR N-BENZYL AMINOCYCLIC THIOUREA LIBRARY

Pool No.	R^1	R^3	R^4
70	X	X	4-dimethylaminobenzoic acid
71	X	X	4-nitrobenzoic acid
72	X	X	3-dimethylaminobenzoic acid
73	X	X	abietic acid
74	X	X	2-methyl-4-nitro-1-imidizole propionic acid
75	X	X	*trans*-styryl acetic acid
76	X	X	cyclopentyl acetic acid
77	X	X	dicyclohexyl acetic acid
78	X	X	(2-pyridylthio)acetic acid
79	X	X	pentadienoic acid
80	X	X	indole-3-acetic acid
81	X	Ala	X
82	X	Phe	X
83	X	Gly	X
84	X	Ile	X
85	X	Leu	X
86	X	Met(O)	X
87	X	Arg (Pmc)	X
88	X	Ser (tBu)	X
89	X	Thr (tBu)	X
90	X	Val	X
91	X	Trp (Boc)	X

TABLE 3

LIBRARY POOL REFERENCE NUMBERS AND VARIABLE R GROUPS FOR N-BENZYL AMINOCYCLIC THIOUREA LIBRARY

Pool No.	R^1	R^3	R^4
92	X	Tyr (Brz)	X
93	X	Tyr (tBu)	X
94	X	ala*	X
95	X	phe	X
96	X	ile	X
97	X	leu	X
98	X	ser	X
99	X	thr (tBu)	X
100	X	val	X
101	X	trp (Boc)	X
102	X	tyr (tBu)	X
103	X	arg (Pmc)	X
104	X	Nle	X
105	X	nle	X
106	X	Nva	X
107	X	nva	X
108	X	Nap	X
109	X	nap	X
110	X	Phg	X
111	X	Glu (tBu)	X
112	X	glu (tBu)	X

TABLE 3

LIBRARY POOL REFERENCE NUMBERS AND VARIABLE R GROUPS FOR N-BENZYL AMINOCYCLIC THIOUREA LIBRARY

Pool No.	R^1	R^3	R^4
113	X	βAla	X
114	X	Cha	X
115	X	cha	X
116	X	His (Trt)	X
117	X	his (Trt)	X
118	Ala	X	X
119	Phe	X	X
120	Gly	X	X
121	Ile	X	X
122	Lys (Boc)	X	X
123	Leu	X	X
124	Met(O)	X	X
125	Asn	X	X
126	Gln	X	X
127	Arg (Pmc)	X	X
128	Ser (tBu)	X	X
129	Thr (tBu)	X	X
130	Val	X	X
131	Trp	X	X
132	Tyr (Brz)	X	X
133	Tyr (tBu)	X	X

TABLE 3

LIBRARY POOL REFERENCE NUMBERS AND VARIABLE R GROUPS FOR N-BENZYL AMINOCYCLIC THIOUREA LIBRARY

Pool No.	R^1	R^3	R^4
134	ala	X	X
135	phe	X	X
136	ile	X	X
137	lys (Boc)	X	X
138	leu	X	X
139	asn	X	X
140	gln	X	X
141	ser	X	X
142	thr (tBu)	X	X
143	val	X	X
144	trp	X	X
145	tyr (tBu)	X	X
146	arg (Pmc)	X	X
147	Nle	X	X
148	nle	X	X
149	Nva	X	X
150	nva	X	X
151	Nap	X	X
152	nap	X	X
153	Phg	X	X
154	Cha	X	X
155	cha	X	X
156	His (Trt)	X	X

TABLE 3			
LIBRARY POOL REFERENCE NUMBERS AND VARIABLE R GROUPS FOR N-BENZYL AMINOCYCLIC THIOUREA LIBRARY			
Pool No.	R^1	R^3	R^4
157	his (Trt)	X	X

*lower case lettering indicates D-amino acids

EXAMPLE IV

This example describes initial biological screens of all 157 library pools as identified in the above Example III. More specifically, this example provides an initial screen of all the N-benzyl aminocyclic thioureas in (1) the anti-microbial assay, (2) the μ-opioid receptor assay and (3) κ-opioid receptor assay, each of which are described in detail above. The results of those screens are provided in Table 4 below. In addition, the results of the μ- and κ-opioid receptor assays are depicted graphically in Figures 3 and 4.

The results of these assays evidence that many of the cyclic urea and thiourea compounds contained within the libraries are biologically active, either as an anti-microbial or inhibitor of a specific opioid receptor. Moreover, the results of the screens provide evidence that there is selectivity of certain compounds for one opioid receptor over another.

TABLE 4

Assays Of The
N-Benzyl Aminocyclic Thiourea Library
(Positional Scanning Format)

Pool No.	Anti-Microbial Assay (IC_{50}, $\mu g/ml$)	μ-Opioid Receptor Assay (% Bound)	κ-Opioid Receptor Assay (% Bound)
1	3.237	6	72
2	6.295	5	46
3	9.792	9	55
4	5.008	6	74
5	<7.8	4	52
6	<7.8	5	84
7	<7.8	5	57
8	<7.8	5	73
9	<7.8	9	72
10	<7.8	10	74
11	<7.8	6	63
12	<7.8	6	83
13	<7.8	11	88
14	<7.8	10	60
15	<7.8	10	66
16	<7.8	8	50
17	10.31	2	71
18	<7.8	17	52
19	<7.8	5	21
20	<7.8	6	47
21	10.31	5	46
22	16.31	3	71
23	<7.8	2	27
24	8.487	11	63
25	NT	7	51
26	8.22	5	43

TABLE 4

Assays Of The
N-Benzyl Aminocyclic Thiourea Library
(Positional Scanning Format)

Pool No.	Anti-Microbial Assay (IC_{50}, $\mu g/ml$)	μ-Opioid Receptor Assay (% Bound)	κ-Opioid Receptor Assay (% Bound)
27	<7.8	7	79
28	<7.8	2	48
29	15.94	7	56
30	<7.8	8	53
31	<7.8	7	103
32	21.14	7	37
33	<7.8	7	22
34	10.31	6	63
35	<7.8	9	50
36	7.926	9	54
37	<7.8	9	38
38	<7.8	9	27
39	<7.8	9	48
40	10.34	6	23
41	<7.8	7	95
42	10.31	5	38
43	12.36	12	49
44	<7.8	6	58
45	<7.8	10	42
46	<7.8	7	30
47	<7.8	7	79
48	18.36	5	51
49	<7.8	5	60
50	<7.8	4	36
51	<7.8	5	65
52	<7.8	6	31

TABLE 4

Assays Of The
N-Benzyl Aminocyclic Thiourea Library
(Positional Scanning Format)

Pool No.	Anti-Microbial Assay (IC_{50}, μg/ml)	μ-Opioid Receptor Assay (% Bound)	κ-Opioid Receptor Assay (% Bound)
53	<7.8	7	30
54	<7.8	8	54
55	<7.8	11	77
56	<7.8	9	36
57	10.31	7	36
58	<7.8	7	35
59	9.004	9	24
60	<7.8	5	56
61	<7.8	14	58
62	8.313	10	35
63	10.31	4	16
64	8.776	12	31
65	9.468	21	55
66	<7.8	12	30
67	<7.8	2	38
68	<7.8	9	60
69	13.85	9	46
70	17.19	11	39
71	8.201	9	30
72	7.757	6	39
73	<7.8	13	29
74	<7.8	9	55
75	15.93	7	39
76	NT	7	76
77	<7.8	14	59
78	<7.8	7	25

TABLE 4

Assays Of The
N-Benzyl Aminocyclic Thiourea Library
(Positional Scanning Format)

Pool No.	Anti-Microbial Assay (IC_{50}, μg/ml)	μ-Opioid Receptor Assay (% Bound)	κ-Opioid Receptor Assay (% Bound)
79	9.985	7	17
80	7.54	7	2
81	10.5	9	43
82	<7.8	11	35
83	5.274	12	62
84	10.31	9	11
85	<7.8	6	6
86	<7.8	8	21
87	<7.8	5	11
88	11.02	20	66
89	9.603	9	65
90	7.719	7	9
91	5.895	8	67
92	8.052	8	47
93	<7.8	10	53
94	8.441	2	37
95	<7.8	5	38
96	<7.8	5	21
97	<7.8	5	19
98	8.925	9	52
99	12.45	10	63
100	<7.8	7	27
101	<7.8	12	108
102	<7.8	8	53
103	<7.8	7	11
104	8.241	4	16

TABLE 4

Assays Of The
N-Benzyl Aminocyclic Thiourea Library
(Positional Scanning Format)

Pool No.	Anti-Microbial Assay (IC_{50}, μg/ml)	μ-Opioid Receptor Assay (% Bound)	κ-Opioid Receptor Assay (% Bound)
105	<7.8	5	9
106	<7.8	6	8
107	7.837	3	7
108	<7.8	11	54
109	<7.8	25	69
110	<7.8	3	26
111	<7.8	7	84
112	<7.8	8	59
113	16.34	9	29
114	<7.8	8	7
115	<7.8	7	12
116	8.097	11	68
117	NT	11	89
118	<7.8	7	38
119	<7.8	7	42
120	<7.8	4	34
121	10.31	9	51
122	9.236	7	1
123	9.562	8	0
124	7.823	8	17
125	<7.8	11	23
126	<7.8	9	15
127	<7.8	15	82
128	<7.8	5	56
129	9.355	4	39
130	10.31	2	31

TABLE 4

Assays Of The
N-Benzyl Aminocyclic Thiourea Library
(Positional Scanning Format)

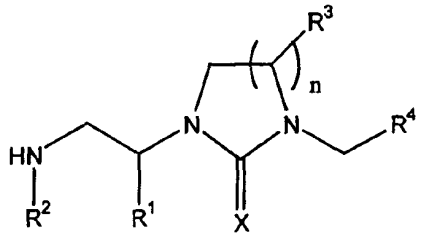
Pool No.	Anti-Microbial Assay (IC_{50}, $\mu g/ml$)	μ-Opioid Receptor Assay (% Bound)	κ-Opioid Receptor Assay (% Bound)
131	<7.8	10	52
132	9.313	4	35
133	<7.8	4	40
134	<7.8	3	39
135	<7.8	5	36
136	9.165	6	40
137	<7.8	3	8
138	<7.8	4	17
139	<7.8	6	22
140	<7.8	3	11
141	<7.8	4	53
142	<7.8	2	50
143	9.798	5	54
144	<7.8	9	39
145	<7.8	3	33
146	13.07	17	60
147	<7.8	5	5
148	<7.8	5	12
149	3.672	4	27
150	8.722	4	13
151	2.415	11	57
152	3.026	11	53
153	5.158	9	25
154	3.46	7	8
155	2.829	8	3
156	5.448	14	40

TABLE 4			
Assays Of The N-Benzyl Aminocyclic Thiourea Library (Positional Scanning Format)			
Pool No.	Anti-Microbial Assay (IC_{50}, μg/ml)	μ-Opioid Receptor Assay (% Bound)	κ-Opioid Receptor Assay (% Bound)
157	9.057	24	107

Although the invention has been described with reference to the examples provided above, it should be understood that various modifications can be made without departing from the spirit of the inventions. Accordingly the invention is limited only by the claims.

WE CLAIM:

1. A combinatorial library comprising two or more cyclic urea compounds of the structure:



wherein:

R^1 is selected from the groups consiting of a hydrogen atom, C_1 to C_{10} alkyl; C_1 to C_{10} substituted alkyl, C_7 to C_{16} phenylalkyl, C_7 to C_{16} substituted phenylalkyl, phenyl, substituted phenyl, C_3 to C_7 cycloalkyl, and C_3 to C_7 substituted cycloalkyl;

R^2 is selected from the group consisting of C_1 to C_{10} alkyl, C_2 to C_{10} alkenyl, benzyl, substituted benzyl, naphthylmethyl, and substituted naphthylmethyl;

R^3 is selected from the group consisting of a hydrogen atom, C_1 to C_{10} alkyl; C_1 to C_{10} substituted alkyl, C_7 to C_{16} phenylalkyl, C_7 to C_{16} substituted phenylalkyl, phenyl, substituted phenyl, C_3 to C_7 cycloalkyl, and C_3 to C_7 substituted cycloalkyl;

R^4 is selected from the group consisting of C_1 to C_{10} alkyl, C_2 to C_{10} alkenyl, C_1 to C_{10} substituted alkyl, C_3 to C_7 substituted cycloalkyl, C_7 to C_{16} phenylalkyl, C_7 to C_{16} substituted phenylalkyl, C_7 to C_{16} phenylalkenyl and C_7 to C_{16} substituted phenylalkenyl;

X is selected from the group consisting of an oxygen atom(O) and a sulfur atom(S); and

n is one or two.

2. The combinatorial library of claim 1, wherein X is an oxygen atom.

3. The combinatorial library of claim 1, wherein X is a sulfur atom.

4. The combinatorial library of claim 1, wherein R^2 is selected from the group consisting of methyl, ethyl, benzyl, allyl, and naphthylmethyl.

5. The combinatorial library of claim 4, wherein R^2 is methyl.

6. The combinatorial library of claim 4, wherein R^2 is benzyl.

7. The combinatorial library of claim 1, wherein

R^1 is selected from the group consisting of methyl, benzyl, hydrogen, 2-butyl, N,N-dimethylaminobutyl, N-methylaminobutyl, 2-methylpropyl, methylsulfinylethyl, N,N-dimethylaminoethyl, N,N-dimethylaminopropyl, N',N',N'-trimethylguanidinopropyl, hydroxymethyl, 1-hydroxyethyl, 2-propyl, N-methyl-3-indolylmethyl, 4-methoxybenzyl, 4-hydroxybenzyl, propyl, butyl, cyclohexylmethyl, phenyl, 2-naphthylmethyl, and 4-imidazolylmethyl;

R^2 is methyl;

R^3 is selected from the group consisting of methyl, benzyl, hydrogen, 3-hydroxypropyl, 2-butyl, N-methylaminobutyl, aminobutyl, 2-methylpropyl, methylsulfinylethyl, guanidinopropyl, hydroxymethyl, 1-hydroxyethyl, 2-propyl, N-methyl-3-indolylmethyl, 4-methoxybenzyl, 4-hydroxybenzyl, propyl, butyl, cyclohexylmethyl, phenyl, 2-naphthylmethyl, and 4-imidazolylmethyl; and

R^4 is selected from the group consisting of 1-phenyl-1-cyclopropylmethyl, 2-phenylbutyl, 3-phenylbutyl, *m*-tolylethyl, 3-fluorophenethyl, 3-bromophenethyl, (α,α,α-trifluoro-*m*-tolyl)ethyl, *p*-tolylethyl, 4-fluorophenethyl, 3-methoxyphenethyl, 4-bromophenethyl, 4-methoxyphenethyl, 4-ethoxyphenethyl, 4-isobutyl-α-methylphenethyl, 3,4-dichlorophenethyl, 3,5-bis(trifluoromethyl)phenethyl, 3-(3,4-dimethoxyphenyl)propyl, 4-biphenethyl, 3-phenyl-2-methyl-2-propenyl, 3-(2-trifluoromethylphenyl)-2-propenyl, 3,4-dimethoxyphenethyl, 3,4-(dihydroxy)phenylethyl, 3-(2-methoxyphenyl)-2-propenyl, benzyl, 3-(4-chlorophenyl)-2-propenyl, *trans*-phenyl-2-propenyl, *m*-xylyl, phenethyl, 3-phenylpropyl, 4-phenylbutyl, 3,5-bis(trifluoromethyl)benzyl, butyl, heptyl, isobutyryl, (+/-)-2-methylbutyl, isovaleryl, 3-methylvaleryl, 4-methylvaleryl, 2-butenyl, 3-butenyl, *p*-xylyl, neopentyl, *tert*-butylethyl, cyclohexylmethyl, cyclohexylethyl, cyclohexylbutyl, cycloheptylmethyl, ethyl, 2-methyl-1-cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, 3-cyclopentylpropyl, cyclohexanepropyl, 4-methyl-1-cyclohexylmethyl, 4-*tert*-butyl-1-cyclohexylmethyl, 4-methylcyclohexylethyl, 2-methyl-2-butenyl, 1-adamantylethyl, 2-(α,α,α-trifluoro-*m*-toluidino)-3-pyridylmethyl, 4-nitrophenethyl, 4-(nitrophenyl)butyl,

3-(4-nitrophenyl)-2-propenyl, 2-nitrobenzyl, 2,4-dinitrophenethyl, 4-biphenethyl, 2-chloro-5-nitrobenzyl, (4-pyridylthio)ethyl, 3,3-diphenylpropyl, 2-chloro-4-nitrobenzyl, 4-dimethylaminobenzyl, 4-nitrobenzyl, 3-dimethylaminobenzyl, abietyl, 2-methyl-4-nitro-1-imidizolylpropyl, *trans*-styrylethyl, cyclopentylethyl, 2,2-dicyclohexylethyl, (2-pyridylthio)ethyl, pentadienyl, and 3-indolylethyl;

X is selected from the group consisting of an oxygen atom(O) and a sulfur atom(S); and

n is one or two.

8. The combinatorial library of claim 7, wherein X is an oxygen atom.

9. The combinatorial library of claim 7, wherein X is a sulfur atom.

10. The combinatorial library of claim 1, wherein:

R^1 is selected from the group consisting of methyl, benzyl, hydrogen, 2-butyl, N-methyl-N-benzylaminobutyl, N-benzylaminobutyl, 2-methylpropyl, methylsulfinylethyl, N,N-dibenzylaminoethyl, N,N-dibenzylaminopropyl, guanidinopropyl, hydroxymethyl, 1-hydroxyethyl, 2-propyl, N-benzyl-3-indolylmethyl, 4-hydroxybenzyl, propyl, butyl, cyclohexylmethyl, phenyl, 2-naphthylmethyl, and 4-imidazolylmethyl;

R^2 is benzyl;

R^3 is selected from the group consisting of methyl, benzyl, hydrogen, 3-hydroxypropyl, 2-butyl, N-methylaminobutyl, aminobutyl, 2-methylpropyl,

methylsulfinylethyl, guanidinopropyl, hydroxymethyl, 1-hydroxyethyl, 2-propyl, N-methyl-3-indolylmethyl, 4-methoxybenzyl, 4-hydroxybenzyl, propyl, butyl, cyclohexylmethyl, phenyl, 2-naphthylmethyl, and 4-imidazolylmethyl;

R^4 is selected from the group consisting of 1-phenyl-1-cyclopropylmethyl, 2-phenylbutyl, 3-phenylbutyl, *m*-tolylethyl, 3-fluorophenethyl, 3-bromophenethyl, (α,α,α-trifluoro-*m*-tolyl)ethyl, *p*-tolylethyl, 4-fluorophenethyl, 3-methoxyphenethyl, 4-bromophenethyl, 4-methoxyphenethyl, 4-ethoxyphenethyl, 4-isobutyl-α-methylphenethyl, 3,4-dichlorophenethyl, 3,5-bis(trifluoromethyl)phenethyl, 3-(3,4-dimethoxyphenyl)propyl, 4-biphenethyl, 3-phenyl-2-methyl-2-propenyl, 3-(2-trifluoromethylphenyl)-2-propenyl, 3,4-dimethoxyphenethyl, 3,4-(dihydroxy)phenylethyl, 3-(2-methoxyphenyl)-2-propenyl, benzyl, 3-(4-chlorophenyl)-2-propenyl, *trans*-phenyl-2-propenyl, *m*-xylyl, phenethyl, 3-phenylpropyl, 4-phenylbutyl, 3,5-bis(trifluoromethyl)benzyl, butyl, heptyl, isobutyryl, (+/-)-2-methylbutyl, isovaleryl, 3-methylvaleryl, 4-methylvaleryl, 2-butenyl, 3-butenyl, *p*-xylyl, neopentyl, tert-butylethyl, cyclohexylmethyl, cyclohexylethyl, cyclohexylbutyl, cycloheptylmethyl, ethyl, 2-methyl-1-cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, 3-cyclopentylpropyl, cyclohexanepropyl, 4-methyl-1-cyclohexylmethyl, 4-tert-butyl-1-cyclohexylmethyl, 4-methylcyclohexylethyl, 2-methyl-2-butenyl, 1-adamantylethyl, 2-(α,α,α-trifluoro-*m*-toluidino)-3-pyridylmethyl, 4-nitrophenethyl, 4-(nitrophenyl)butyl, 3-(4-nitrophenyl)-2-propenyl, 2-nitrobenzyl, 2,4-dinitrophenethyl, 4-biphenethyl, 2-chloro-5-nitrobenzyl, (4-pyridylthio)ethyl, 3,3-diphenylpropyl,

2-chloro-4-nitrobenzyl, 4-dimethylaminobenzyl, 4-nitrobenzyl, 3-dimethylaminobenzyl, abietyl, 2-methyl-4-nitro-1-imidizolylpropyl, *trans*-styrylethyl, cyclopentylethyl, 2,2-dicyclohexylethyl, (2-pyridylthio)ethyl, pentadienyl, and 3-indolylethyl;

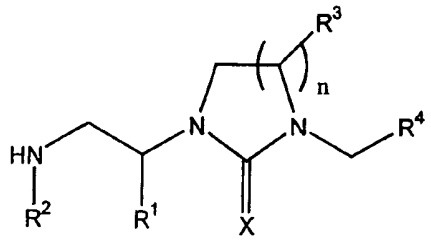
X is selected from the group consisting of an oxygen atom(O) and a sulfur atom(S); and

n is one or two.

11. The combinatorial library of claim 10, wherein X is an oxygen atom.

12. The combinatorial library of claim 10, wherein X is a sulfur atom.

13. A single cyclic urea compound of the structure:



wherein:

R^1 is selected from the groups consiting of a hydrogen atom, C_1 to C_{10} alkyl; C_1 to C_{10} substituted alkyl, C_7 to C_{16} phenylalkyl, C_7 to C_{16} substituted phenylalkyl, phenyl, substituted phenyl, C_3 to C_7 cycloalkyl, and C_3 to C_7 substituted cycloalkyl;

R^2 is selected from the group consisting of C_1 to C_{10} alkyl, C_2 to C_{10} alkenyl, benzyl, substituted benzyl, naphthylmethyl, and substituted naphthylmethyl;

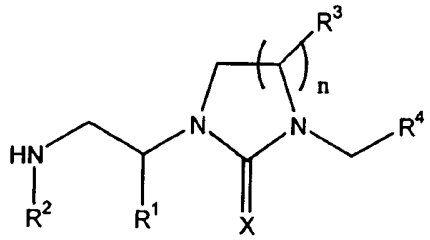
R^3 is selected from the group consisting of a hydrogen atom, C_1 to C_{10} alkyl; C_1 to C_{10} substituted alkyl, C_7 to C_{16} phenylalkyl, C_7 to C_{16} substituted phenylalkyl, phenyl, substituted phenyl, C_3 to C_7 cycloalkyl, and C_3 to C_7 substituted cycloalkyl;

R^4 is selected from the group consisting of C_1 to C_{10} alkyl, C_2 to C_{10} alkenyl, C_1 to C_{10} substituted alkyl, C_3 to C_7 substituted cycloalkyl, C_7 to C_{16} phenylalkyl, C_7 to C_{16} substituted phenylalkyl; C_7 to C_{16} phenylalkenyl and C_7 to C_{16} substituted phenylalkenyl;

X is selected from the group consisting of an oxygen atom(O) and a sulfur atom(S); and

n is one.

14. A single cyclic urea compound of the structure:



wherein:

R^1 is selected from the groups consiting of a hydrogen atom, C_1 to C_{10} alkyl; C_1 to C_{10} substituted alkyl, C_7 to C_{16} phenylalkyl, C_7 to C_{16} substituted phenylalkyl,

phenyl, substituted phenyl, C_3 to C_7 cycloalkyl, and C_3 to C_7 substituted cycloalkyl;

R^2 is selected from the group consisting of C_1 to C_{10} alkyl, C_2 to C_{10} alkenyl, benzyl, substituted benzyl, naphthylmethyl, and substituted naphthylmethyl;

R^3 is selected from the group consisting of C_1 to C_{10} alkyl; C_1 to C_{10} substituted alkyl, C_7 to C_{16} phenylalkyl, C_7 to C_{16} substituted phenylalkyl, phenyl, substituted phenyl, C_3 to C_7 cycloalkyl, and C_3 to C_7 substituted cycloalkyl;

R^4 is selected from the group consisting of C_1 to C_{10} alkyl, C_2 to C_{10} alkenyl, C_1 to C_{10} substituted alkyl, C_3 to C_7 substituted cycloalkyl, C_7 to C_{16} phenylalkyl, C_7 to C_{16} substituted phenylalkyl; C_7 to C_{16} phenylalkenyl and C_7 to C_{16} substituted phenylalkenyl;

X is selected from the group consisting of an oxygen atom(O) and a sulfur atom(S); and

n is two.

15. The compound of claims 13 or 14, wherein

R^1 is selected from the group consisting of methyl, benzyl, hydrogen, 2-butyl, N,N-dimethylaminobutyl, N-methylaminobutyl, 2-methylpropyl, methylsulfinylethyl, N,N-dimethylaminoethyl, N,N-dimethylaminopropyl, N',N',N'-trimethylguanidinopropyl, hydroxymethyl, 1-hydroxyethyl, 2-propyl, N-methyl-3-indolylmethyl, 4-methoxybenzyl, 4-hydroxybenzyl, propyl, butyl, cyclohexylmethyl, phenyl, 2-naphthylmethyl, and 4-imidazolylmethyl;

R^2 is methyl;

R^3 is selected from the group consisting of methyl, benzyl, hydrogen, 3-hydroxypropyl, 2-butyl, N-methylaminobutyl, aminobutyl, 2-methylpropyl, methylsulfinylethyl, guanidinopropyl, hydroxymethyl, 1-hydroxyethyl, 2-propyl, N-methyl-3-indolylmethyl, 4-methoxybenzyl, 4-hydroxybenzyl, propyl, butyl, cyclohexylmethyl, phenyl, 2-naphthylmethyl, and 4-imidazolylmethyl; and

R^4 is selected from the group consisting of 1-phenyl-1-cyclopropylmethyl, 2-phenylbutyl, 3-phenylbutyl, *m*-tolylethyl, 3-fluorophenethyl, 3-bromophenethyl, (α,α,α-trifluoro-*m*-tolyl)ethyl, *p*-tolylethyl, 4-fluorophenethyl, 3-methoxyphenethyl, 4-bromophenethyl, 4-methoxyphenethyl, 4-ethoxyphenethyl, 4-isobutyl-α-methylphenethyl, 3,4-dichlorophenethyl, 3,5-bis(trifluoromethyl)phenethyl, 3-(3,4-dimethoxyphenyl)propyl, 4-biphenethyl, 3-phenyl-2-methyl-2-propenyl, 3-(2-trifluoromethylphenyl)-2-propenyl, 3,4-dimethoxyphenethyl, 3,4-(dihydroxy)phenylethyl, 3-(2-methoxyphenyl)-2-propenyl, benzyl, 3-(4-chlorophenyl)-2-propenyl, *trans*-phenyl-2-propenyl, *m*-xylyl, phenethyl, 3-phenylpropyl, 4-phenylbutyl, 3,5-bis(trifluoromethyl)benzyl, butyl, heptyl, isobutyryl, (+/-)-2-methylbutyl, isovaleryl, 3-methylvaleryl, 4-methylvaleryl, 2-butenyl, 3-butenyl, *p*-xylyl, neopentyl, *tert*-butylethyl, cyclohexylmethyl, cyclohexylethyl, cyclohexylbutyl, cycloheptylmethyl, ethyl, 2-methyl-1-cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, 3-cyclopentylpropyl, cyclohexanepropyl, 4-methyl-1-cyclohexylmethyl, 4-*tert*-butyl-1-cyclohexylmethyl, 4-methylcyclohexylethyl, 2-methyl-2-butenyl, 1-adamantylethyl, 2-(α,α,α-trifluoro-*m*-toluidino)-3-pyridylmethyl, 4-nitrophenethyl, 4-(nitrophenyl)butyl,

3-(4-nitrophenyl)-2-propenyl, 2-nitrobenzyl, 2,4-dinitrophenethyl, 4-biphenethyl, 2-chloro-5-nitrobenzyl, (4-pyridylthio)ethyl, 3,3-diphenylpropyl, 2-chloro-4-nitrobenzyl, 4-dimethylaminobenzyl, 4-nitrobenzyl, 3-dimethylaminobenzyl, abietyl, 2-methyl-4-nitro-1-imidizolylpropyl, *trans*-styrylethyl, cyclopentylethyl, 2,2-dicyclohexylethyl, (2-pyridylthio)ethyl, pentadienyl, and 3-indolylethyl; and

X is selected from the group consisting of an oxygen atom(O) and a sulfur atom(S).

16. The compound of claims 13 or 14, wherein

R^1 is selected from the group consisting of methyl, benzyl, hydrogen, 2-butyl, N-methyl-N-benzylaminobutyl, N-benzylaminobutyl, 2-methylpropyl, methylsulfinylethyl, N,N-dibenzylaminoethyl, N,N-dibenzylaminopropyl, guanidinopropyl, hydroxymethyl, 1-hydroxyethyl, 2-propyl, N-benzyl-3-indolylmethyl, 4-hydroxybenzyl, propyl, butyl, cyclohexylmethyl, phenyl, 2-naphthylmethyl, and 4-imidazolylmethyl;

R^2 is benzyl;

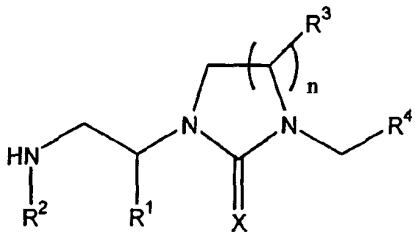
R^3 is selected from the group consisting of methyl, benzyl, hydrogen, 3-hydroxypropyl, 2-butyl, N-methylaminobutyl, aminobutyl, 2-methylpropyl, methylsulfinylethyl, guanidinopropyl, hydroxymethyl, 1-hydroxyethyl, 2-propyl, N-methyl-3-indolylmethyl, 4-methoxybenzyl, 4-hydroxybenzyl, propyl, butyl, cyclohexylmethyl, phenyl, 2-naphthylmethyl, and 4-imidazolylmethyl;

R^4 is selected from the group consisting of 1-phenyl-1-cyclopropylmethyl, 2-phenylbutyl, 3-phenylbutyl,

m-tolylethyl, 3-fluorophenethyl, 3-bromophenethyl, (α,α,α-trifluoro-*m*-tolyl)ethyl, *p*-tolylethyl, 4-fluorophenethyl, 3-methoxyphenethyl, 4-bromophenethyl, 4-methoxyphenethyl, 4-ethoxyphenethyl, 4-isobutyl-α-methylphenethyl, 3,4-dichlorophenethyl, 3,5-bis(trifluoromethyl)phenethyl, 3-(3,4-dimethoxyphenyl)propyl, 4-biphenethyl, 3-phenyl-2-methyl-2-propenyl, 3-(2-trifluoromethylphenyl)-2-propenyl, 3,4-dimethoxyphenethyl, 3,4-(dihydroxy)phenylethyl, 3-(2-methoxyphenyl)-2-propenyl, benzyl, 3-(4-chlorophenyl)-2-propenyl, *trans*-phenyl-2-propenyl, *m*-xylyl, phenethyl, 3-phenylpropyl, 4-phenylbutyl, 3,5-bis(trifluoromethyl)benzyl, butyl, heptyl, isobutyryl, (+/-)-2-methylbutyl, isovaleryl, 3-methylvaleryl, 4-methylvaleryl, 2-butenyl, 3-butenyl, *p*-xylyl, neopentyl, *tert*-butylethyl, cyclohexylmethyl, cyclohexylethyl, cyclohexylbutyl, cycloheptylmethyl, ethyl, 2-methyl-1-cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, 3-cyclopentylpropyl, cyclohexanepropyl, 4-methyl-1-cyclohexylmethyl, 4-*tert*-butyl-1-cyclohexylmethyl, 4-methylcyclohexylethyl, 2-methyl-2-butenyl, 1-adamantylethyl, 2-(α,α,α-trifluoro-*m*-toluidino)-3-pyridylmethyl, 4-nitrophenethyl, 4-(nitrophenyl)butyl, 3-(4-nitrophenyl)-2-propenyl, 2-nitrobenzyl, 2,4-dinitrophenethyl, 4-biphenethyl, 2-chloro-5-nitrobenzyl, (4-pyridylthio)ethyl, 3,3-diphenylpropyl, 2-chloro-4-nitrobenzyl, 4-dimethylaminobenzyl, 4-nitrobenzyl, 3-dimethylaminobenzyl, abietyl, 2-methyl-4-nitro-1-imidizolylpropyl, *trans*-styrylethyl, cyclopentylethyl, 2,2-dicyclohexylethyl, (2-pyridylthio)ethyl, pentadienyl, and 3-indolylethyl; and

X is an oxygen atom(O) or a sulfur atom(S).

17. A single cyclic urea compound of the structure:



wherein:

R^1 is selected from the groups consiting of a hydrogen atom, C_1 to C_{10} alkyl; C_1 to C_{10} substituted alkyl, C_7 to C_{16} phenylalkyl, C_7 to C_{16} substituted phenylalkyl, phenyl, substituted phenyl, C_3 to C_7 cycloalkyl, and C_3 to C_7 substituted cycloalkyl;

R^2 is selected from the group consisting of C_1 to C_{10} alkyl, C_2 to C_{10} alkenyl, benzyl, substituted benzyl, naphthylmethyl, and substituted naphthylmethyl;

R^3 is selected from the group consisting of a hydrogen atom, C_1 to C_{10} alkyl; C_1 to C_{10} substituted alkyl, C_7 to C_{16} phenylalkyl, C_7 to C_{16} substituted phenylalkyl, phenyl, substituted phenyl, C_3 to C_7 cycloalkyl, and C_3 to C_7 substituted cycloalkyl;

R^4 is selected from the group consisting of 1-phenyl-1-cyclopropylmethyl, 2-phenylbutyl, 3-phenylbutyl, *m*-tolylethyl, 3-fluorophenethyl, 3-bromophenethyl, (α,α,α-trifluoro-*m*-tolyl)ethyl, *p*-tolylethyl, 4-fluorophenethyl, 3-methoxyphenethyl, 4-bromophenethyl, 4-methoxyphenethyl, 4-ethoxyphenethyl, 4-isobutyl-α-

methylphenethyl, 3,4-dichlorophenethyl, 3,5-bis(trifluoromethyl)phenethyl, 3-(3,4-dimethoxyphenyl)propyl, 4-biphenethyl, 3-phenyl-2-methyl-2-propenyl, 3-(2-trifluoromethylphenyl)-2-propenyl, 3,4-dimethoxyphenethyl, 3,4-(dihydroxy)phenylethyl, 3-(2-methoxyphenyl)-2-propenyl, benzyl, 3-(4-chlorophenyl)-2-propenyl, *trans*-phenyl-2-propenyl, *m*-xylyl, phenethyl, 3-phenylpropyl, 4-phenylbutyl, 3,5-bis(trifluoromethyl)benzyl, butyl, heptyl, isobutyryl, (+/-)-2-methylbutyl, isovaleryl, 3-methylvaleryl, 4-methylvaleryl, 2-butenyl, 3-butenyl, *p*-xylyl, neopentyl, *tert*-butylethyl, cyclohexylmethyl, cyclohexylethyl, cyclohexylbutyl, cycloheptylmethyl, ethyl, 2-methyl-1-cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, 3-cyclopentylpropyl, cyclohexanepropyl, 4-methyl-1-cyclohexylmethyl, 4-*tert*-butyl-1-cyclohexylmethyl, 4-methylcyclohexylethyl, 2-methyl-2-butenyl, 1-adamantylethyl, 2-(α,α,α-trifluoro-*m*-toluidino)-3-pyridylmethyl, 4-nitrophenethyl, 4-(nitrophenyl)butyl, 3-(4-nitrophenyl)-2-propenyl, 2-nitrobenzyl, 2,4-dinitrophenethyl, 4-biphenethyl, 2-chloro-5-nitrobenzyl, (4-pyridylthio)ethyl, 3,3-diphenylpropyl, 2-chloro-4-nitrobenzyl, 4-dimethylaminobenzyl, 4-nitrobenzyl, 3-dimethylaminobenzyl, abietyl, 2-methyl-4-nitro-1-imidizolylpropyl, *trans*-styrylethyl, cyclopentylethyl, 2,2-dicyclohexylethyl, (2-pyridylthio)ethyl, pentadienyl, and 3-indolylethyl;

X is selected from the group consisting of an oxygen atom(O) and a sulfur atom(S); and

n is two.

18. The compound of claims 13, 14 or 17, wherein R^2 is selected from the group consisting of methyl, ethyl, benzyl, allyl, and naphthylmethyl.

19. The compound of claim 18, wherein R^2 is methyl.

20. The compound of claim 18, wherein R^2 is benzyl.

21. The compound of claim 17, wherein

R^1 is selected from the group consisting of methyl, benzyl, hydrogen, 2-butyl, N,N-dimethylaminobutyl, N-methylaminobutyl, 2-methylpropyl, methylsulfinylethyl, N,N-dimethylaminoethyl, N,N-dimethylaminopropyl, N',N',N'-trimethylguanidinopropyl, hydroxymethyl, 1-hydroxyethyl, 2-propyl, N-methyl-3-indolylmethyl, 4-methoxybenzyl, 4-hydroxybenzyl, propyl, butyl, cyclohexylmethyl, phenyl, 2-naphthylmethyl, and 4-imidazolylmethyl;

R^2 is methyl;

R^3 is selected from the group consisting of methyl, benzyl, hydrogen, 3-hydroxypropyl, 2-butyl, N-methylaminobutyl, aminobutyl, 2-methylpropyl, methylsulfinylethyl, guanidinopropyl, hydroxymethyl, 1-hydroxyethyl, 2-propyl, N-methyl-3-indolylmethyl, 4-methoxybenzyl, 4-hydroxybenzyl, propyl, butyl, cyclohexylmethyl, phenyl, 2-naphthylmethyl, and 4-imidazolylmethyl; and

X is selected from the group consisting of an oxygen atom(O) and a sulfur atom(S).

22. The compound of claim 17, wherein

R^1 is selected from the group consisting of methyl, benzyl, hydrogen, 2-butyl, N-methyl-N-benzylaminobutyl, N-benzylaminobutyl, 2-methylpropyl, methylsulfinylethyl, N,N-dibenzylaminoethyl, N,N-dibenzylaminopropyl, guanidinopropyl, hydroxymethyl, 1-hydroxyethyl, 2-propyl, N-benzyl-3-indolylmethyl, 4-hydroxybenzyl, propyl, butyl, cyclohexylmethyl, phenyl, 2-naphthylmethyl, and 4-imidazolylmethyl;

R^2 is benzyl;

R^3 is selected from the group consisting of methyl, benzyl, hydrogen, 3-hydroxypropyl, 2-butyl, N-methylaminobutyl, aminobutyl, 2-methylpropyl, methylsulfinylethyl, guanidinopropyl, hydroxymethyl, 1-hydroxyethyl, 2-propyl, N-methyl-3-indolylmethyl, 4-methoxybenzyl, 4-hydroxybenzyl, propyl, butyl, cyclohexylmethyl, phenyl, 2-naphthylmethyl, and 4-imidazolylmethyl; and

X is an oxygen atom(O) or a sulfur atom(S).

23. The compound of claims 13, 14, 15, 16, 17, 21 or 22, wherein X is an oxygen atom.

24. The compound of claims 13, 14, 15, 16, 17, 21 or 22, wherein X is a sulfur atom.

REACTION SCHEME I

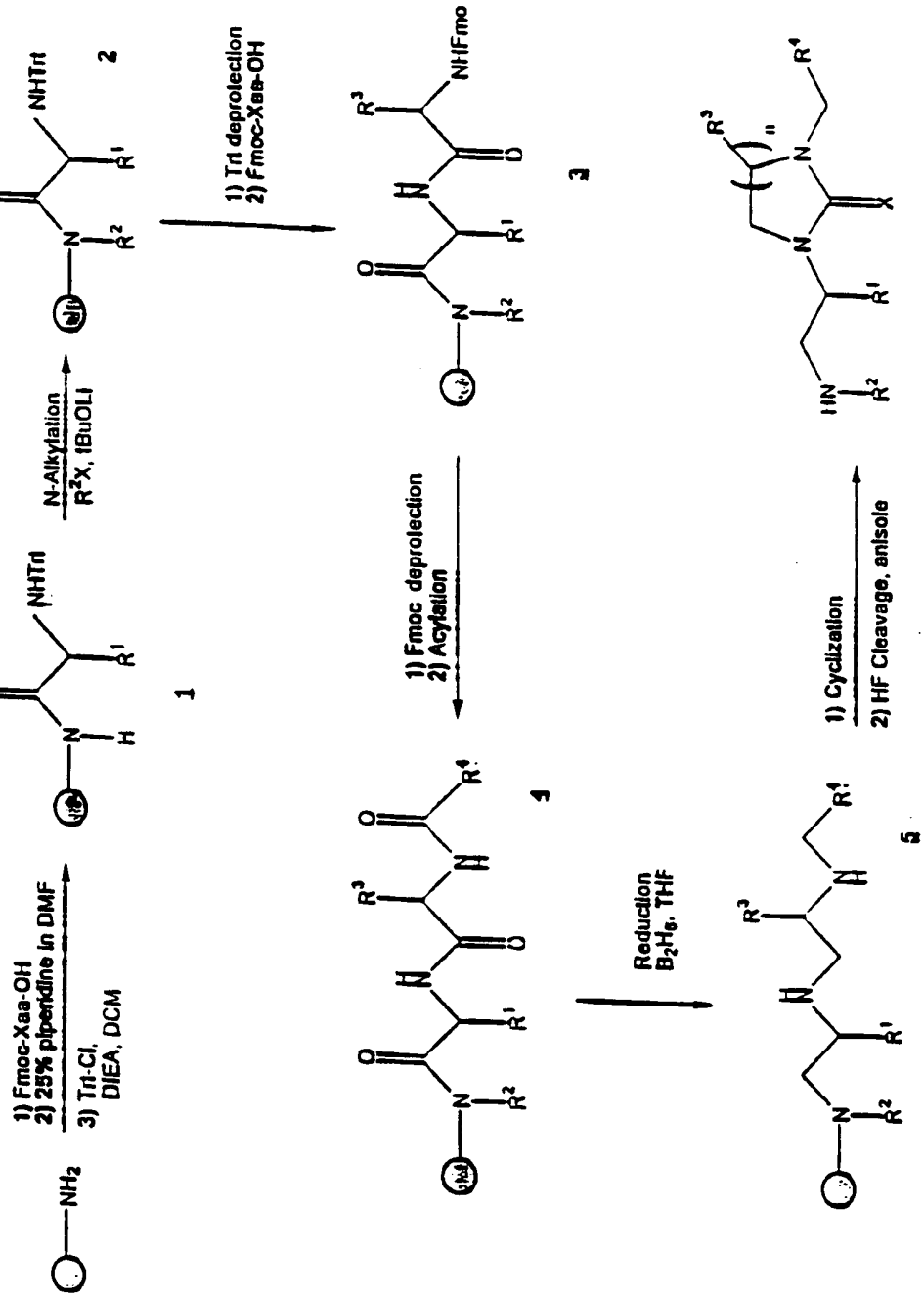
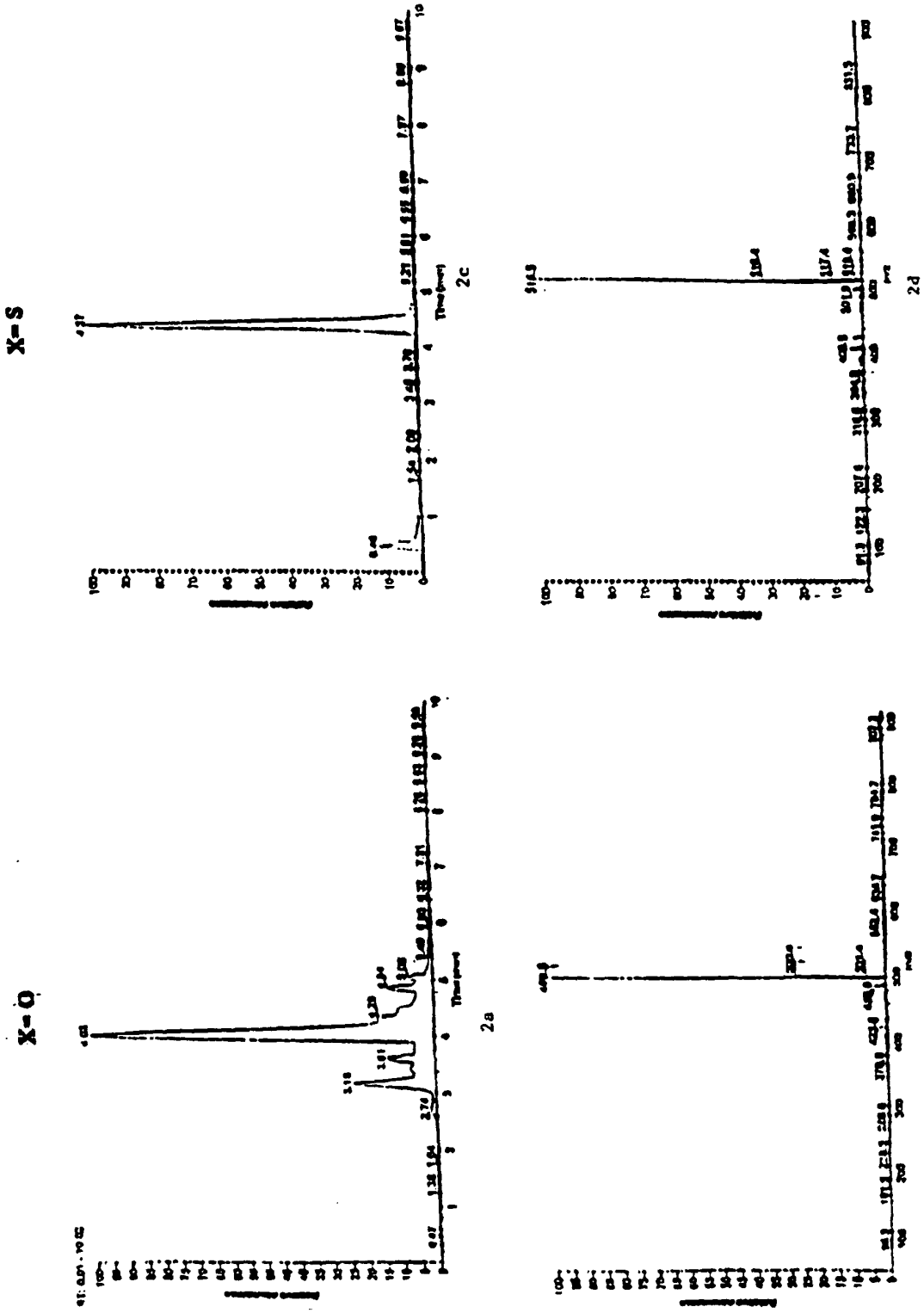
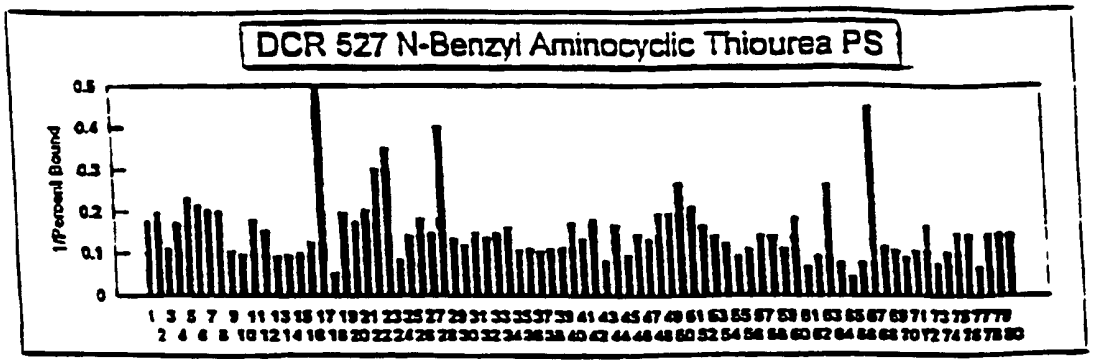
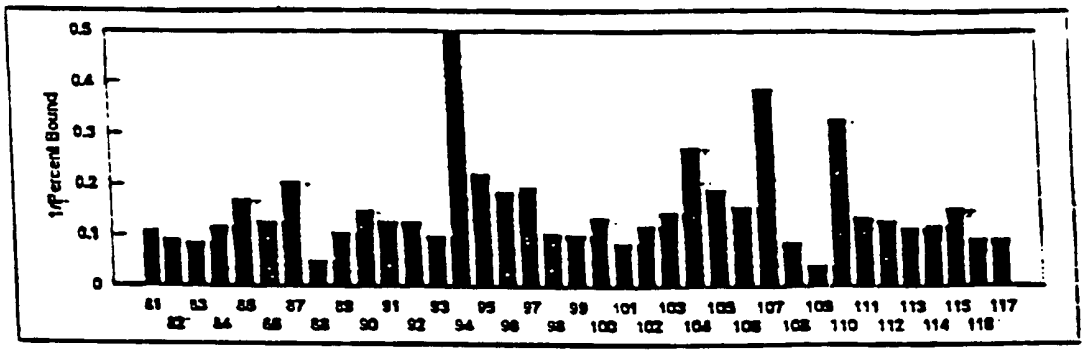


Figure 1

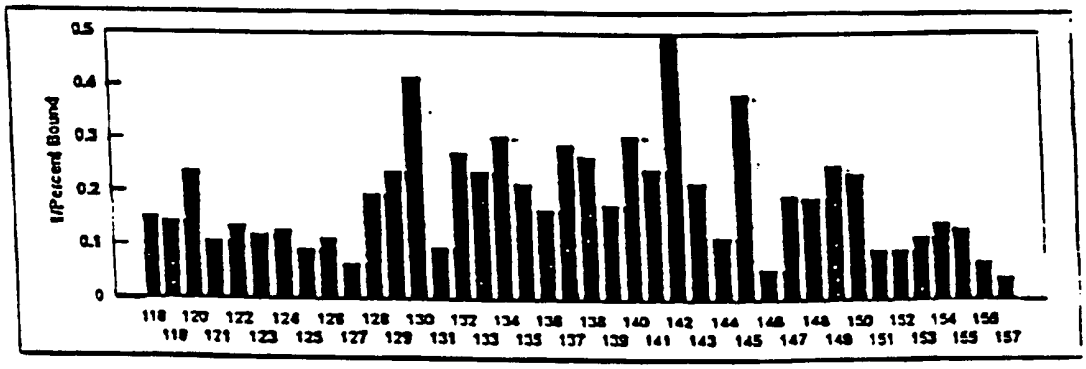

X=S
X=O
2c
2d
2a



3a

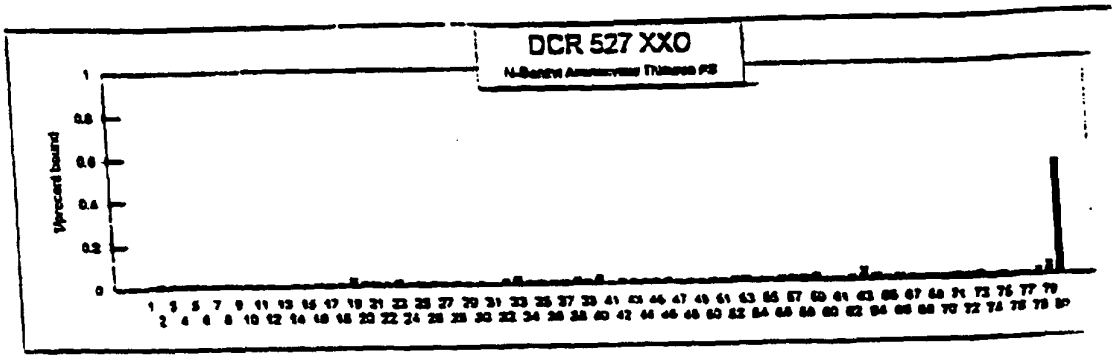


3b

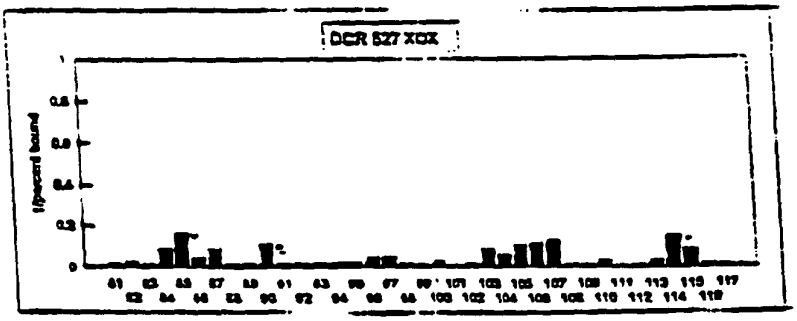


3c

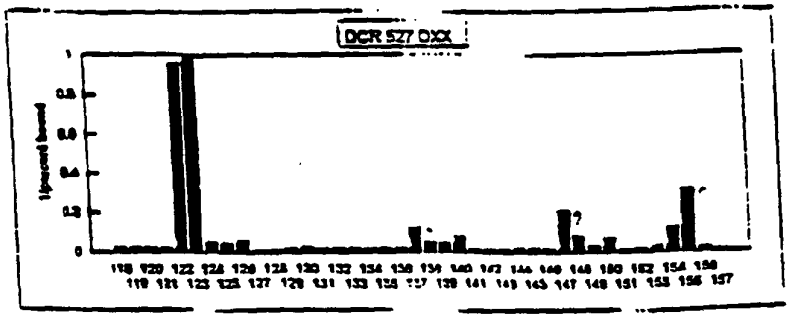
Figure 3



4a



4b



4c

Figure 4

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/19945

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 38/12; C07K 17/00

US CL :Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 530/317, 331, 334; 548/316.4, 317.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Chem abstr., Vol. 86, Issue No. 0009-2258. 31 January 1977, page 364, column 2, Abstract No. 86:29756n, SINGH, H. et al. Studies in potential filaricides: Part VIII. Syntheses of 1-ethyl-3-(2-dialkylaminoethyl)- and 1,3-diethyl-4-dialkylaminomethylhexahydropyrimidin-2-ones. Indian J. Chem. Sect. B 1976, 14B(7), 528-31 (Eng).	1, 2, 4-6 and 13
A	KIM J. et al. Synthesis of a Cyclic Urea as a Nonnatural Biopolymer Scaffold. Tetrahedron Letters. 22 July 1996 Vol. 37, No. 30, pages 5309-5312.	1-17

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
07 JANUARY 1998	06 FEB 1998
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer BENNETT CELSA Telephone No. (703) 308-0196

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/19945

A. CLASSIFICATION OF SUBJECT MATTER:
US CL : 530/317, 331, 334; 548/316.4, 317.1